CLINICAL, ELECTROPHYSIOLOGICAL, LABORATORY PREDICTORS (INCLUDING SERUM CORTISOL) OF RESPIRATORY FAILURE IN GUILLAIN-BARRE SYNDROME PATIENTS

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CERTIFICATE

This is to certify that the dissertation entitled "**CLINICAL, ELECTROPHYSIOLOGICAL, LABORATORY, PREDICTORS (INCLUDING SERUM CORTISOL) OF RESPIRATORY FAILURE IN GUILLAIN-BARRE´ SYNDROME PATIENTS"** is a bonafide work done by **Dr. SUGAN GANDHI.T**, at Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai in partial fulfilment of the university rules and regulations for award of M.D., Degree in General Medicine (Branch-I) under my guidance and supervision during the academic year 2009 -2012.

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LIST OF ABBREVIATIONS

AIDP-Acute Inflammatory Demyelinating Polyneuropathy

AMAN-Acute Motor Axonal Neuropathy

AMSAN-Acute Motor Sensory Axonal Neuropathy

CAD-Coronary Artery Disease

CMAP-Compound Motor Action Potential

CMV-Cytomegalovirus

CSF- Cerebrospinal Fluid

DM-Diabetes Mellitus

DML-Distal Motor Latency

ELISA-Enzyme Linked Immunosorbent Assay

EMG-Electromyography

GBS-Guillain–Barré Syndrome

GIT-Gastrointestinal tract

HIV-Human Immunodeficiency Virus

HT/SHT-Systemic Hypertension

IVIG- Intravenous Immunoglobulin

MNCV-Motor Nerve Conduction Velocity

MRC-Medical Research Council

MRI-Magnetic Resonance Imaging

NCS-Nerve Conduction Study

PE-Plasma Exchange

PT-Pulmonary Tuberculosis

SBCT- Single Breath Count Test

SLE- Systemic Lupus Erythematosis

SNAP-Sensory Nerve Action Potential

SNCV-Sensory Nerve Conduction Velocity

TTPD-Time to Peak Disability

URI-Upper Respiratory Illness

CONTENTS

Sl.No.	TITLE	Page No.
I	INTRODUCTION	1
II	AIM OF THE STUDY	3
III	REVIEW OF LITERATURE	4
IV	MATERIALS AND METHODS	22
V	OBSERVATION AND RESULTS	28
VI	DISCUSSION	53
VIII	CONCLUSION	64
IX	BIBLIOGRAPHY	
X	ANNEXURE	
	i. PROFORMA	
	ii. MASTER CHART	
	iii. ETHICAL COMMITTEE CLEARANCE CERTIFICATE	

INTRODUCTION

The Guillain–Barré syndrome is one of the most common forms of polyneuropathy[1].It is the commonest cause of acute flaccid quadriparesis. It can present with varying degrees of motor weakness, from mild weakness to total paralysis and respiratory failure.

It has an unpredictable clinical course with upto 30% of patients requiring assisted ventilation during the course of their illness[2]. Successful management mandates anticipation, prompt recognition and optimal treatment of neuromuscular respiratory failure in GBS[3].

While inherently unpredictable, the course of patients with severe GBS can, to some extent, be predicted on the basis of clinical information like bilateral facial weakness, autonomic dysfunction and bulbar weakness[1,3,4].

Few studies have shown that measurement of baseline plasma cortisol levels can be helpful for early detection of patients with Guillain–Barré syndrome at risk for respiratory failure at least 24 hrs later[5].

Also electrophysiological tests are helpful for assessing risk of respiratory failure. However early indicators of subsequent progression to respiratory failure have not been clearly established.

This study is undertaken to find whether clinical laboratory and electrodiagnostic factors could help in predicting respiratory failure and hence the need for mechanical ventilation in GBS patients.

These data may be helpful in the decisions regarding admission to the intensive care unit and preparation for elective intubation.

AIM AND OBJECTIVE

AIM

1. To assess the clinical presentation and the subsequent manifestations including decline in respiratory effort among 50 GBS patients admitted at Rajiv Gandhi Government General Hospital, Chennai.

2. To do laboratory tests including serum cortisol and electrophysiological tests among 50 GBS patients admitted at Rajiv Gandhi Government General Hospital, Chennai.

OBJECTIVE

To identify clinical, laboratory and electrophysiological features associated with progression to respiratory failure in GBS.

REVIEW OF LITERATURE

INTRODUCTION

Guillain–Barré syndrome (GBS) is an acute, frequently severe, and fulminant polyradiculoneuropathy that is autoimmune in nature[6,7].

GBS is the most common cause of acute or subacute generalized paralysis[2].

HISTORY

The earliest description of an afebrile generalized paralysis is probably that of Wardrop and Ollivier, in 1834. Then in 1859, Octave Landry reported an acute, ascending, predominantly motor paralysis with respiratory failure, leading to death[8,9]. Hence GBS is sometimes called Landry's paralysis. This was followed by Osler description of afebrile polyneuritis in 1892[2].

However this syndrome is named after the French physicians Guillain, Barré and Strohl, who in 1916, emphasized the main clinical features of GBS: motor weakness, areflexia, paresthesias with minor sensory loss, and increased protein in CSF without pleocytosis (albumin cytological dissociation)[10].They reported on two soldiers who developed an acute paralysis associated with loss of muscle stretch reflexes.

The first comprehensive account of the pathology of GBS was that of Haymaker and Kernohan (1949), who stressed that edema of the nerve roots was an important change in the early stages of the disease[11]. Asbury, Arnason, and

Adams (1969) established that the essential lesion, from the beginning of the disease, is a perivascular mononuclear inflammatory infiltration of the roots and nerves[12].

SYNONYMS

- Acute post-infective polyradiculoneuropathy.
- Acute infectious polyneuritis.
- Landry–Guillain–Barré–Strohl syndrome
- Post-infective polyneuritis

INCIDENCE

It occurs in all parts of the world and in all seasons, affecting children and adults of all ages and both sexes[2]. Males are at slightly higher risk for GBS than females (1.5:1)[7], and in Western countries adults are more frequently affected than children[1,6]. The crude average annual incidence rate varies in different countries from 0.6 to 1.9 per 100,000 people[13]. The mean age of onset is around 40 but many series have shown a bimodal distribution with peaks in the third and sixth decades of life[1]. Cases are known in infants and in the very aged[2].

DIAGNOSTIC CRITERIA

The diagnosis of GBS depends on clinical criteria supported by electrophysiological studies and CSF findings[7].

Diagnostic criteria of AIDP was given by Asbury and Cornblath in 1990[8,7,6,14].

I. Required for Diagnosis

1. Progressive weakness of variable degree from mild paresis to complete paralysis

2. Generalized hypo- or areflexia

II.Supportive of Diagnosis

1. Clinical Features

a. Symptom progression: Motor weakness rapidly progresses initially but ceases by 4 weeks. Nadir attained by 2 weeks in 50%, 3 weeks 80%, and 90% by 4 weeks.

b. Demonstration of relative limb symmetry regarding paresis.

c. Mild to moderate sensory signs.

d. Frequent cranial nerve involvement: Facial (cranial nerve VII) 50% and typically bilateral but asymmetric; occasional involvement of cranial nerves XII, X, and occasionally III, IV, and VI as well as XI.

e. Recovery typically begins 2–4 weeks following plateau phase.

f. Autonomic dysfunction can include tachycardia, other arrhythmias, postural hypotension, hypertension, other vasomotor symptoms.

g. A preceding gastrointestinal illness (e.g., diarrhoea) or upper respiratory tract infection is common.

2. Cerebrospinal Fluid Features Supporting Diagnosis

a. Elevated or serial elevation of CSF protein.

b. CSF cell counts are <10 mononuclear cell/mm^3.

3. Electrodiagnostic Medicine Findings Supportive of Diagnosis

a.80% of patients have evidence of NCV slowing/conduction block at some time during disease process.

b. Patchy reduction in NCV attaining values less than 60% of normal.

c. Distal motor latency increase may reach 3 times normal values.

d. F-waves indicate proximal NCV slowing.

e. About 15–20% of patients have normal NCV findings.

f. No abnormalities on nerve conduction studies may be seen for several weeks.

III. Findings Reducing Possibility of Diagnosis

1. Asymmetric weakness

2. Failure of bowel/bladder symptoms to resolve

3. Severe bowel/bladder dysfunction at initiation of disease

4. Greater than 50 mononuclear cells/mm^3 in CSF

5. Well-demarcated sensory level

IV. Exclusionary Criteria

1. Diagnosis of other causes of acute neuromuscular weakness (e.g., myasthenia gravis, botulism, poliomyelitis, toxic neuropathy).

2. Abnormal CSF cytology suggesting carcinomatous invasion of the nerve roots.

SUBTYPES

Griffin et al. in 1996 proposed a tentative classification of GBS subtypes based on the clinical picture and electrophysiological and pathological findings[15].

- Acute inflammatory demyelinating polyradiculoneuropathy.
- Acute motor axonal neuropathy.
- Acute motor sensory axonal neuropathy.
- Miller-Fisher syndrome.
- Acute pandysautonomia.
- Sensory GBS.

The most common variant is acute inflammatory demyelinating polyneuropathy (AIDP)[6]. There are two axonal variants, which are often clinically severe – the acute motor axonal neuropathy (AMAN) and acute motor sensory axonal neuropathy (AMSAN) subtypes[6,7].

A range of limited or regional GBS syndromes are also encountered. Notable among these are the Miller Fisher syndrome (MFS), Bickerstaff's encephalitis, acute pandysautonomia, polyneuritiscranialis, pharyngeal-cervical-brachial variant often with ptosis, oculopharyngeal weakness, bilateral facial or abducens weakness with distal paraesthesias. Other atypical presentations are areflexic paraparesis, Miller Fisher syndrome coupled with weakness of bulbar or arm muscles and Isolated arm weakness.

The Miller-Fisher syndrome (MFS), which accounts for 5% of cases, is characterized by ophthalmoplegia, ataxia, and areflexia[48]. Ocular signs range from complete ophthalmoplegia, including dilated and unreactive pupils, to external ophthalmoparesis with or without ptosis. Cranial nerves other than ocular motor nerves may be affected. Motor strength is characteristically preserved, although overlap with typical GBS seems to occur.

ANTECEDENT EVENTS

Infections

Over half of Guillain–Barré syndrome patients experience symptoms of viral respiratory or gastrointestinal infections during the 1–3 weeks prior to the onset of neurological symptoms[16,32].

The neurological illness is preceded by symptoms of respiratory tract infection in approximately 40% and gastrointestinal infection in less than 20% in an English series; 8% had undergone an operation in the preceding 3 months[16]Serological studies have implicated a wide range of infective agents. Cytomegalovirus (13%) and Campylobacter jejuni (in approximately 30%) are the most common. Epstein–Barr virus (10%), Mycoplasma pneumoniae (5%), human immunodeficiency virus (HIV), and childhood exanthems are also reported[16,17,18,19]. Others include varicella zoster virus, hepatitis A and B, and Haemophilus influenza, lymes disease, human herpes virus. The most common identifiable

bacterial organism linked to GBS and particularly its axonal forms is Campylobacter jejuni[7]. GBS associated with cytomegalovirus tends to occur in younger patients, with a high occurrence of respiratory muscle weakness, cranial nerve involvement, and significant sensory involvement[20]. By contrast, *Campylobacter jejuni* infection is associated with preceding diarrhoeal illness in 70%, a pure motor disorder (AMAN) is common, and recovery can be markedly slow[19]. Forms of Guillain–Barré syndrome precipitated by both campylobacter and cytomegalovirus show delayed recovery compared to cases unassociated with these two infections[19].

Recent Immunization

After immunization in 1976 of more than 40 million adults in the United States with swine influenza virus vaccine (A/New Jersey/76) more than 500 cases of Guillain–Barré syndrome were reported in vaccinated individuals[2]. Influenza vaccines in use from 1992 to 1994, however, resulted in only one additional case of GBS per million persons vaccinated, and the more recent seasonal influenza vaccines appear to confer a GBS risk of <1 per million[6].No other causal relationship linking Guillain–Barré syndrome to vaccination with other strains of influenza virus has been shown. A prospective case-control study in England showed no significant excess of any form of vaccination during the 3 months preceding the Guillain–Barré syndrome[18].

Others

- Systemic lupus erythematosus (SLE).
- Lymphoma (including Hodgkin's disease).[21]
- Exposure to thrombolytic agents.
- Drugs, including streptokinase, suramin, gangliosides, and heroin.
- Trauma and surgery.
- After renal transplantation from a cytomegalovirus-positive donor.
- In pharmacologically immunosuppressed patients after solid organ or bone marrow transplantation.

IMMUNOPATHOGENESIS

GBS results from immune responses to non self antigens (infectious agents, vaccines) that misdirect to host nerve tissue through a resemblance-of-epitope (molecular mimicry) mechanism[6]. It is likely that both cellular and humoral immune mechanisms contribute to tissue damage in AIDP[22].The neural targets are likely to be glycoconjugates, specifically gangliosides. Guillain–Barré syndrome bears a strong histological resemblance to experimental allergic neuritis, an acute monophasic disorder induced by immunization of experimental animals with peripheral-nerve myelin proteins, particularly P2 and galactocerebroside[24].

Antiganglioside antibodies, most frequently to GM1, are common in GBS (20–50% of cases), particularly in those preceded by C. jejuni infection[6,7]. Anti-GQ1b

IgG antibodies are found in >90% of patients with MFS[6,7]in cases of AMAN antibodies against GD1a appear to have a fine specificity that favors binding to motor rather than sensory nerve roots, even though this ganglioside is expressed on both fiber types[6].The peripheral nerves may be affected at all levels from the roots to distal intramuscular motor nerve endings, although the majority of the lesions usually occur on the ventral roots, proximal spinal nerves, and lower cranial nerves[7].

CLINICAL FEATURES

GBS manifests as a rapidly evolving areflexic motor paralysis with or without sensory disturbance. The fairly symmetrical weakness of the lower limbs ascends proximally over hours to several days and may subsequently involve arm, facial, and oropharyngeal muscles, and in severe cases, respiratory muscles. Hyporeflexia or areflexia are the invariable features of GBS but may be absent early in the course of the disease[7].Total areflexia occurs in over 80% of patients at some stage of the illness. The remainder usually lose their ankle jerks in isolation[25].

The proportion of patients developing respiratory failure and requiring assisted ventilation ranges from 12% in epidemiological series to 30% in hospital-based series[6,7].The need for mechanical ventilation is associated a rapid tempo of progression, and the presence of facial and/or bulbar weakness and a rapid decline

in vital capacity[3,4,6,8,26,50]. Serial measures of decline in respiratory function that could predict future respiratory failure included vital capacity of less than 20 mL/kg or a decline by 30% from baseline, maximal inspiratory pressure less than 30 cm, and maximal expiratory respiratory pressure of less than 40 cm of H_2O. This so-called 20–30–40 rule allows patients at risk to be identified and transferred to an intensive care unit for even closer monitoring[8]. In a series of 200 patients, short disease duration, inability to lift the head from bed, and a vital capacity of less than 60% predicted the need for mechanical ventilation in 85% of patients with all three risk factors[28]. Ropper and Kehne's established criteria for intubation, it includes bulbar weakness, vital capacity <15ml/kg, and pO_2on room air <70mm Hg[52]. When respiratory assistance is needed for longer than 2 weeks, a tracheostomy should be performed.

Approximately half the patients develop cranial-nerve palsies, usually in the wake of severe ascending limb weakness[25, 26]. Facial paresis, usually bilateral, is found in at least in 50% of patients[7]. Involvement of extraocular muscles and lower cranial nerves is seen less often. Fever and constitutional symptoms are absent at the onset and, if present, cast doubt on the diagnosis.

In three-quarters of patients, the first neurological symptom is of paraesthesia in the toes, less often in the fingers[2].Cutaneous sensory deficits (e.g., loss of pain and temperature sensation) are usually relatively mild, but functions

subserved by large sensory fibers, such as deep tendon reflexes and proprioception, are more severely affected. Sensory loss is frequently limited to the distal impairment of vibration sense.When sensory signs are present, they usually consist of impaired vibration and joint-position sensations[25].

Urinary retention occurs in about 15% of patients soon after the onset of weakness[2], but is usually transient. Once clinical worsening stops and the patient reaches a plateau (almost always within 4 weeks of onset), further progression is unlikely.

Autonomic dysfunction is common in the Guillain–Barré syndrome, occurring in over 60%[29]. Most of the clinically significant autonomic dysfunction occurs within the first 2–4 weeks of the illness, the peak period of paralysis[7].

It is related to either increased or decreased sympathetic-parasympathetic activity, resulting in orthostatic hypotension, urinary retention, gastrointestinal atony, iridoplegia, episodic or sustained hypertension, sinus tachycardia, tachyarrhythmias, anhidrosis or episodic diaphoresis, and acral vasoconstriction. Excessive vagal activity accounts for sudden episodes of bradycardia, heart block, and asystole. Serious cardiac arrhythmias with hemodynamic instability tend to be more frequent in patients with severe quadriparesis and respiratory failure[7]. Arrhythmias, cause or contribute to death in 7% patients[30,31].

Plasma cortisol and catecholamines were found to be raised in patients with dysautonomia presenting as hypertension and tachycardia[49].Autonomic dysfunction can result in electrocardiographical changes including T-wave abnormalities, ST-segment depression, QRS widening, QT prolongation, and various forms of heart block[7].

Pain in the neck, shoulder, back, or diffusely over the spine is also common in the early stages of GBS, occurring in 50% of patients[6]. Interscapular or low back pain with radiation into the legs is most common[7].

Other pains in GBS include dysesthetic pain in the extremities as a manifestation of sensory nerve fiber involvement and a deep aching pain may be present in weakened muscles. These pains are self-limited and often respond to standard analgesics.

Papilloedema occasionally develops. If so, it is sometimes associated with headache and raised spinal fluid pressure and tends to occur after a delay of some weeks[25,33]. Optic neuritis and pyramidal tract signs are other rare manifestations which may point to a mild associated acute disseminated encephalomyelitis [34].

Recurrent Guillain–Barré syndrome occurs in up to 3%, often after an interval of many years[26].

LABORATORY STUDIES

CSF findings are distinctive, consisting of an elevated CSF protein level [1–10 g/L (100–1000 mg/dL)] without accompanying pleocytosis[6].In the first week of neurological symptoms the CSF protein may be normal but then becomes elevated on subsequent examinations. In approximately 10% of cases, the CSF protein remains normal throughout the illness[7].

A transient increase in the CSF white cell count (10–100/µL) occurs on occasion in otherwise typical GBS; however, a sustained CSF pleocytosis suggests an alternative diagnosis (viral myelitis) or a concurrent diagnosis such as unrecognized HIV infection, leukemia or lymphoma with infiltration of nerves, or neurosarcoidosis[6].

Mild transient elevations in liver enzymes without obvious cause are found in approximately one third of patients. Hyponatremia is seen most frequently in ventilated patients because of inappropriate secretion of antidiuretic hormone. Deposition of immune complexes may rarely lead to glomerulonephritis and result in microscopic haematuria and proteinuria[7].

Elevated serum antibodies to Mycoplasma, CMV, or *C. jejuni* can pinpoint the preceding infection. Preceding *C. jejuni* infection has been linked to axonal variants, worse outcome, and high titers of anti-GM1, anti-GD1b, anti-GD1a, and

anti-GalNAc-GD1a ganglioside antibodies of the IgG class[37]. Elevated anti-GQ1b ganglioside antibodies are consistently found in MFS.

ELECTRODIAGNOSTIC STUDIES

Abnormalities of electrophysiological studies are found in approximately 90% of established cases[7].

The hallmark of demyelinating polyneuropathies is a widespread increase in conduction time caused by impaired salutatory conduction. Therefore, NCS findings are characterized by significant slowing of conduction velocities (less than 75% of the lower limit of normal) and distal latencies (greater than 130% of the upper limit of normal).The most common electrophysiological abnormalities in GBS include prolonged distal motor and F-wave latencies, absent or impersistent F waves, conduction block, reduction in distal CMAP amplitudes with or without temporal dispersion, and slowing of motor conduction velocities[36].

Electrodiagostic features are mild or absent in the early stages of GBS and lag behind the clinical evolution. Absent H-reflexes, delayed or absent F-waves, and low-amplitude or absent SNAPs in the upper extremity, combined with normal sural SNAPs, are changes supportive of the diagnosis in the first week of the illness[36]. Within the first 2 weeks, the most common findings are of mildly prolonged distal motor latencies and of conduction block [35]. In cases with axonal degeneration, reduced CMAP and SNAP amplitudes are found, more markedly in

the lower extremities with conduction velocities and distal latencies being usually normal.

Needle EMG initially shows decreased motor unit recruitment. Subsequently, if any amount of axonal degeneration occurs, fibrillation potentials appear 2–4 weeks after onset. Lumbosacral spinal MRI may demonstrate gadolinium enhancement of lumbar roots.

DIFFERENTIAL DIAGNOSIS

I. Acute neuropathies

- Hepatic porphyrias
- Critical illness neuropathy
- Diphtheria
- Toxins
- Arsenic, thallium, organophosphates, lead
- Neurotoxic fish and shellfish poisoning (ciguatoxin, tetrodotoxin, saxitoxin)
- Buckthorn
- Tick paralysis
- Vasculitis
- Inflammatory meningoradiculopathies
- Lyme disease, cytomegalovirus lumbosacral radiculomyelopathy

II. Disorders of neuromuscular junction

- Botulism, myasthenia gravis

III. Myopathies

- Hypokalemia, hypophosphatemia
- Rhabdomyolysis
- Polymyositis
- Intensive care myopathy

IV. Central nervous system disorders

- Poliomyelitis
- West Nile virus poliomyelitis
- Rabies
- Transverse myelitis
- Acute brainstem infarct
- spinal cord compression

TREATMENT

Treatment should be initiated as soon as possible after diagnosis. 2 weeks after the first motor symptom, it is not known whether immunotherapy is still effective[6]. If the patient has already reached the plateau stage, then treatment probably is no longer indicated, unless the patient has severe motor weakness.

Either high-dose intravenous immune globulin (IVIg) or plasmapheresis can be initiated, as they are equally effective for typical GBS. A combination of the two therapies is not significantly better than either alone.

IVIg is often the initial therapy chosen because of its ease of administration and good safety record. Intravenous immunoglobulin (IvIg)given at 0.4 g/kg body weight/day for 5 days, is at least equally effective as plasma exchange[42,43].There is some evidence that GBS autoantibodies are neutralized by anti-idiotypic antibodies present in IVIg preparations, perhaps accounting for the therapeutic effect.

A course of plasmapheresis usually consists of 40–50 mL/kg plasma exchange (PE) 4–5 times over a week. Meta-analysis of randomized clinical trials indicates that treatment reduces the need for mechanical ventilation by nearly half (from 27% to 14% with PE) and increases the likelihood of full recovery at 1 year (from 55% to 68%)[38,39,40,41]. Significant improvement may occur toward the end of the first week of treatment, or may be delayed for several weeks.

The lack of noticeable improvement following a course of IVIg or PE is not an indication to treat with the alternate treatment.

About 10% of patients treated by plasma exchange will subsequently undergo a mild relapse between 5 and 42 days later, which may be treated by a further course of plasma exchange[44]. As with plasma exchange, IvIg-treated patients may deteriorate secondarily within 2 weeks of treatment[45].

Neither oral steroids nor intravenous high-dose steroids have a place in treating the Guillain–Barré syndrome[46]. A randomized trial of oral prednisolone therapy suggested that steroids might increase the subsequent relapse rate[47].

Occasional patients with very mild forms of GBS, especially those who appear to have already reached a plateau when initially seen, may be managed conservatively without IVIg or PE.

In the worsening phase of GBS, most patients require monitoring in a critical care setting, with particular attention to vital capacity, heart rhythm, blood pressure, nutrition, deep vein thrombosis prophylaxis, cardiovascular status, early consideration (after 2 weeks of intubation) of tracheotomy, and chest physiotherapy. Frequent turning and assiduous skin care are important, as are daily range-of-motion exercises to avoid joint contractures and daily reassurance as to the generally good outlook for recovery.

MATERIALS AND METHODS

STUDY DESIGN

Cross sectional study

STUDY MATERIAL

The study was conducted on 50 Guillain–Barré syndrome patients admitted in the Institute of Internal medicine, Rajiv Gandhi Government General Hospital, Chennai.

INCLUSION CRITERIA

All adult patients who fulfilled standard diagnostic criteria for Guillain-Barre syndrome as given by Asbury and Cornblath[8,7,6,14] were included in the study.

EXCLUSION CRITERIA

1. Any patient admitted with asymmetrical weakness and preserved reflexes.
2. Any patient with fever at the onset of symptoms.
3. Any patient admitted with clinical or laboratory features of hypokalemic paralysis.
4. Any patient in whom the weakness progressed for more than 4 weeks.
5. Any patient admitted with features of upper motor neuron signs and symptoms.
6. Any patient with a definite level of sensory loss or predominant sensory symptoms in the absence of muscle weakness.
7. Any patient admitted with history of bite preceding the illness.

8. Any patient admitted with history of exposure to toxins.
9. Patients with predominant/persistent bladder /bowel symptoms.
10. Diagnosis of other causes of acute neuromuscular weakness (e.g., myasthenia gravis, botulism, poliomyelitis, toxic neuropathy).
11. Abnormal CSF cytology suggesting carcinomatous invasion of the nerve roots
12. Patients already intubated/ventilated while admitting in our hospital.
13. Patients on steroid therapy.

METHODOLOGY

In all 50 patients,

1. Detailed history including demographic factors, personal habits, preceding illnesses, co morbid illnesses, and clinical features was taken.
2. Detailed neurological examination including higher mental functions, cranial nerves, motor system, sensory system and autonomic system was done everyday during hospitalization.

Motor power was assessed according to Medical Research Council grading. Autonomic dysfunction was looked for in all these patients. History of postural giddiness (if ambulant), palpitation/tremors, excessive sweating/hypohydrosis, nausea, vomiting, constipation, diarrhoea, fecal/urinary incontinence, urinary/retention, dry mouth/dry eyes were specifically asked for.

Frequent blood pressure measurement was done in lying and sitting posture and if possible in standing posture to bring out orthostatic hypotension in ambulant patients. Resting pulse and pulse variability in lying and sitting posture and if possible in standing posture was done. Assessment of heart rate variability to deep breathing and valsalva was done in selected cases. Continuous BP, pulse and electrocardiographic (ECG) monitoring was done in intubated patients. Examination of eyes for pupillary abnormalities and dryness was done along with examination of skin and mouth.

3. Bedside methods to detect the respiratory insufficiency were done in all patients at least 3 times daily, everyday during hospitalization, including breath-holding time, single breath count and chest expansion. Of which single breath count was widely used.

Single breath count test (SBCT) has been used to evaluate the ventilatory status of patients with suspected neuromuscular compromise (e.g.,myasthenia gravis, Guillain–Barre syndrome, and botulism)[55].

The test is performed by having the patient count out loud after taking one deep breath. Most adults with normal ventilatory function are able to count to 50 in a single breath[54,55].

If the patient can count to "10" on one breath they likely have a forced vital capacity of about 1000 ml, if they can count to "25" then the vital capacity can be

estimated at about 2000 ml.In general a single breath count of <15 is consistent with significant impairment of the patient's vital capacity[54,55,56].

4. Time to peak disability was assessed in all patients. Time to peak disability was defined as time to intubation (patients who underwent ventilation), or time to worst score on the MRC grading of muscle power (patients who did not undergo ventilation) from onset of neuropathic symptoms.

5. Basic investigations like complete blood count, blood sugar and urea, serum creatinine and electrolytes, erythrocyte sedimentation rate, liver function tests, electrocardiogram and chest x-ray were done in all patients.

6. Microbiological, Biochemical and cytological analysis of CSF was done in all patients.

7. Serum cortisol level was analysed within 24 hours of admission in all patients.

8. Nerve conduction study was done in patients whomever it was possible.

Nerve conduction study was conducted by using the machine RMS. Nerve conduction studies were done in both upper (ulnar and median nerve) and lower limbs (posterior tibial nerve and peroneal nerve).These evaluated F waves (absence, latency, chrono dispersion) in multiple motor nerves and H reflex (amplitude, latency) on stimulation of Posterior Tibial nerve.

Motor nerve conduction studies included assessment of CMAP amplitude, distal motor latency (DML) and motor nerve conduction velocity (MNCV)along

with assessment for temporal dispersion and conduction block. Antidromic studies on median, ulnar, and sural nerve yielded sensory nerve conduction studies including sensory nerve action potential (SNAP) and sensory nerve conduction velocity (SNCV).

Standard criteria, in comparison with standards for the particular laboratory, were applied to label a particular value as abnormal. Distal motor latency was prolonged if it was more than 150% of upper limit of normal. Motor conduction velocity was slowed if it was less than 70% of lower limit of normal and F wave latency was prolonged if more than 150% of upper limit of normal. Conduction block implied a 30% drop in CMAP amplitude on proximal stimulation as compared to distal stimulation, and temporal dispersion implied a 20% increase in CMAP dispersion on proximal stimulation, both these parameters indicating a proximal conduction block. Electrophysiological data were classified according to Hadden and colleagues[53] definition as primary demyelinating, primary axonal, unexcitable, equivocal, or normal.

These demographic, clinical, laboratory, electrodiagnostic tests data were recorded in a standard proforma. These data were analysed between patients who subsequently developed respiratory failure and those who did not develop respiratory failure.

Association of these demographic, clinical, laboratory, electrodiagnostic factors with respiratory failure was tested using Fisher's exact test, $\chi 2$ test and Student t test.

The study was approved by the institutional ethics committee of the hospital.

OBSERVATION AND RESULTS

Fifty patients were included in our study. Demographic factors analysed were age, sex, co-morbid illnesses (DM, HT, respiratory illnesses), habits like smoking and alcoholism and antecedent events either preceding fever, upper respiratory illness, gastrointestinal illness, or other risk factors.

AGE DISTRIBUTION: The age distribution of 50 patients was as follows.

TABLE 1: AGE DISTRIBUTION

AGE(in years)	NO. OF PATIENTS	PERCENTAGE
11–20	2	4%
21–30	9	18%
31–40	14	28%
41–50	12	24%
51–60	9	18%
61–70	3	6%
71–80	1	2%
Total	50	

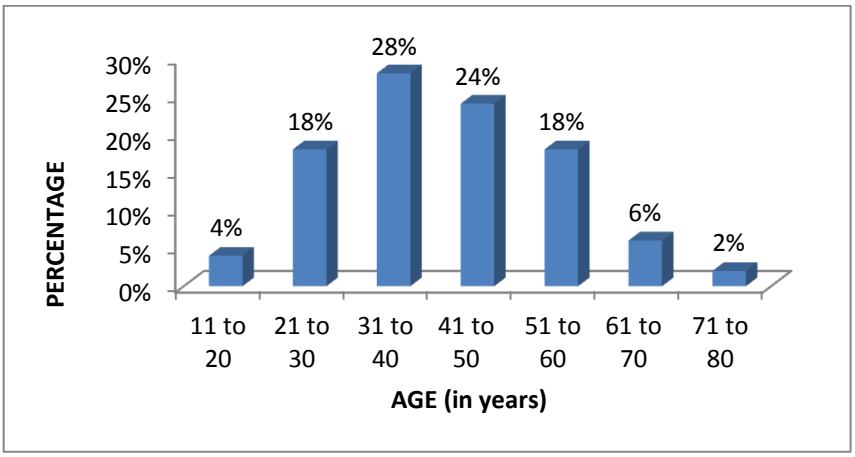


FIGURE 1: GRAPH SHOWING AGE DISTRIBUTION

All of them were between the age group of 15–75 years. The peak incidence was in the age group of 31 to 40 years and the median was 40 years.

Age distribution of patients with and without respiratory failure was as shown below in Table 2.

TABLE 2: COMPARISON OF AGE AND RESPIRATORY FAILURE

AGE (in years)	RESPIRATORY FAILURE No. of Patients (%)	NO RESPIRATORY FAILURE No. of Patients (%)
<30	4(37%)	7(63%)
30–60	21(60%)	14(40%)
60–90	2(50%)	2(50%)

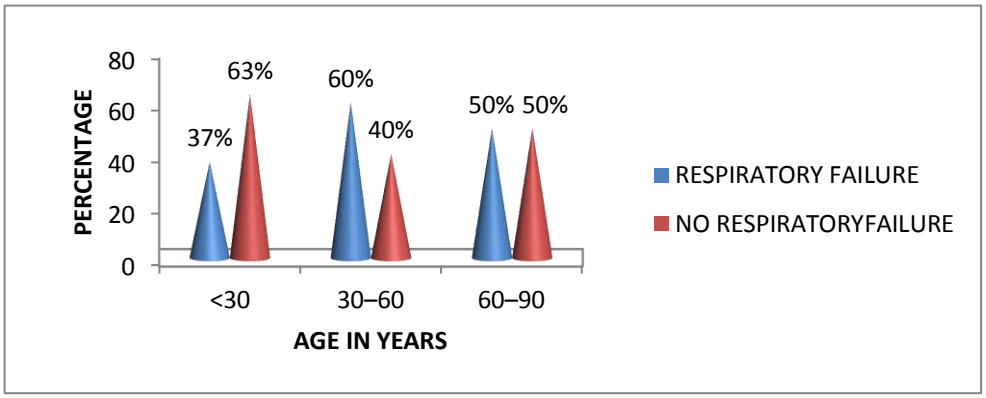


FIGURE 2: GRAPH SHOWING COMPARISON OF AGE AND RESPIRATORY FAILURE

Though 60% of persons in the age group 30–60 years developed respiratory failure, it did not reach statistical significance ($\chi 2$ test p=0.23)

SEX DISTRIBUTION:

Of the 50 patients, 31 were males and 19 were females.

TABLE 3: SEX DISTRIBUTION

SEX	NO. OF INDIVIDUALS	PERCENTAGE
Males	31	62%
Females	19	38%

Among them 18 males and 9 females developed respiratory failure.

TABLE 4: COMPARISON OF SEX AND RESPIRATORY FAILURE

SEX	RESPIRATORY FAILURE No. of Patients(%)	NO RESPIRATORY FAILURE No. of Patients(%)
Males	18(58%)	13(42%)
Females	9(48%)	10(52%)

$\chi 2$ test p=0.56

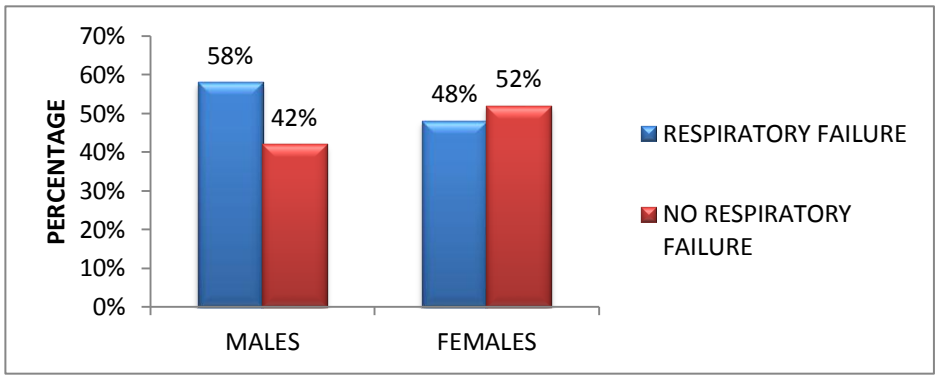


FIGURE 3: GRAPH SHOWING COMPARISON OF SEX AND RESPIRATORY FAILURE

When the influence of sex on the development of respiratory failure was analysed we found that sex did not influence the development of respiratory failure ($\chi 2$ test p=0.56)

CO–MORBID ILLNESSES AND HABITS

Among the 50 patients, 12 were diabetics, 8 were hypertensives, 2 were asthmatics, 2 were coronary artery disease patients and 3 were treated pulmonary tuberculosis patients.

TABLE 5: INCIDENCE OF CO MORBID ILLNESSES

CO–MORBID ILLNESS	NO. OF PATIENTS
DM	12
SHT	8
Bronchial asthma	2
CAD	2
Treated PT	3

Among the 12 diabetics, 9 developed respiratory failure and among the 38 non-diabetics, 18 developed respiratory failure.

TABLE 6: COMPARISON OF DIABETES MELLITUS AND RESPIRATORY FAILURE

	RESPIRATORY FAILURE No. of Patients	NO RESPIRATORY FAILURE No. of patients
DM	9	3
No DM	18	20

$\chi 2$ test P= 0.11

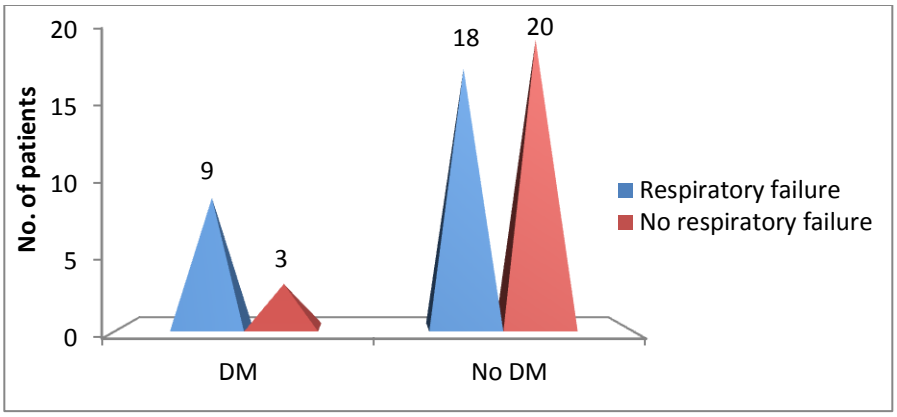


FIGURE 4: GRAPH SHOWING COMPARISON OF DM AND RESPIRATORY FAILURE

There were 8 hypertensive patients of which 6 patients and 21 among the 42 non- hypertensive patients developed respiratory failure.

TABLE 7: COMPARISON OF HYPERTENSION AND RESPIRATORY FAILURE

	RESPIRATORY FAILURE No. of patients	NO RESPIRATORY FAILURE No. of patients
HT	6	2
No HT	21	21

Fischer's exact test, p=0.26

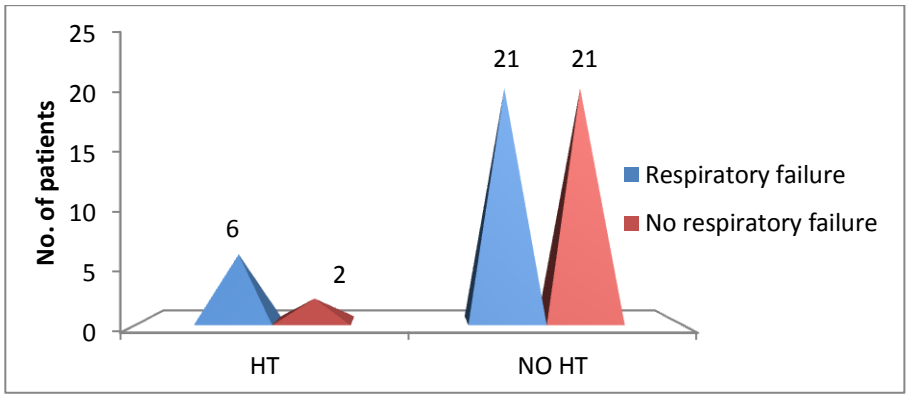


FIGURE 5: GRAPH SHOWING COMPARISON OF HT AND RESPIRATORY FAILURE

Among the 5 patients with preceding respiratory illness, 2 developed respiratory failure.

TABLE 8: COMPARISON OF RESPIRATORY ILLNESS AND RESPIRATORY FAILURE

	RESPIRATORY FAILURE No. of patients(%)	NO RESPIRATORY FAILURE No. of patients(%)
RESPIRATORY ILLNESS	2(40%)	3(60%)
NO RESPIRATORY ILLNESS	25(56%)	20(44%)

Fischer's exact test, p=0.65

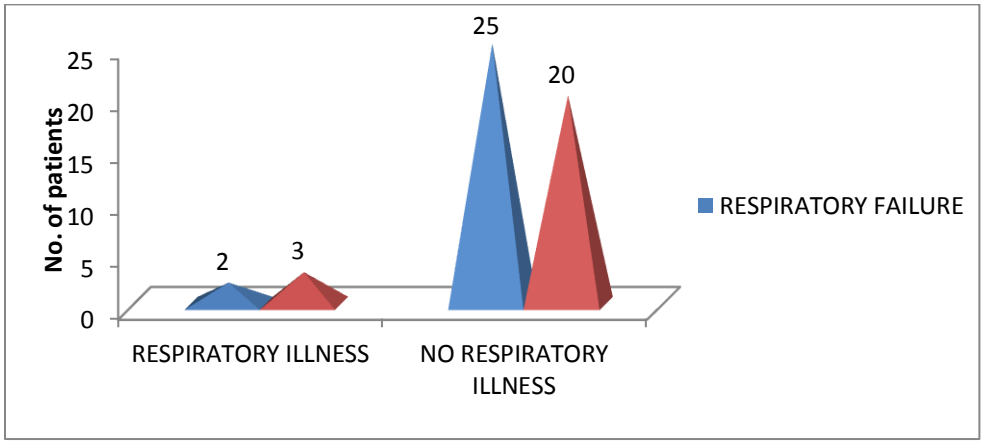


FIGURE 6: GRAPH SHOWING COMPARISON OF RESPIRATORY ILLNESS AND RESPIRATORY FAILURE

On analysing the co morbid illnesses it was found that co-morbid illnesses like diabetes (P=0.11), hypertension (P=0.26) or preceding respiratory illnesses (P=0.65) did not influence the development of respiratory failure.

Among the 50 patients, there were 13 smokers and 6 alcoholics, of which 8 smokers and 3 alcoholics developed respiratory failure.

TABLE 9: COMPARISON OF SMOKING AND RESPIRATORY FAILURE

	RESPIRATORY FAILURE No. of Patients	NO RESPIRATORY FAILURE No. of Patients
SMOKING	8	5
NO SMOKING	19	18

Fischer's exact test, p= 0.75

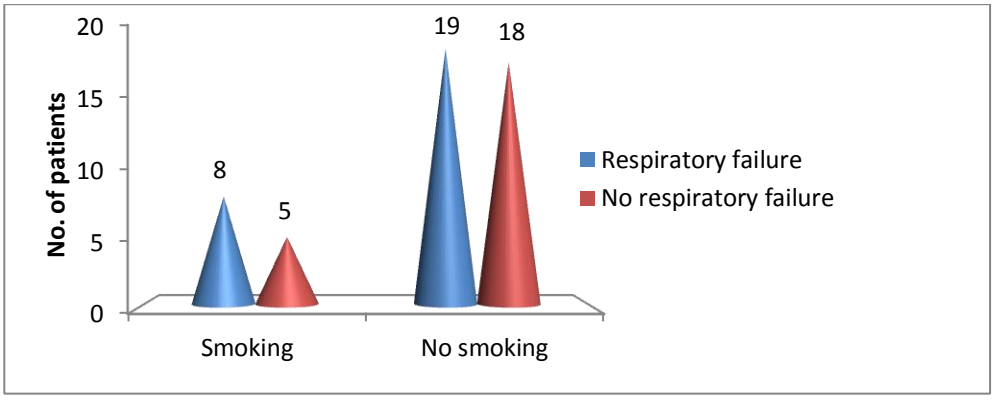


FIGURE 7: GRAPH SHOWING COMPARISON OF SMOKING AND RESPIRATORY FAILURE

TABLE 10: COMPARISON OF ALCOHOLISM AND RESPIRATORY FAILURE

	RESPIRATORY FAILURE No. of Patients	NO RESPIRATORY FAILURE No.of Patients
ALCOHOLISM	3	3
NO ALCOHOLISM	24	20

Fischer's exact test, p= 1.00

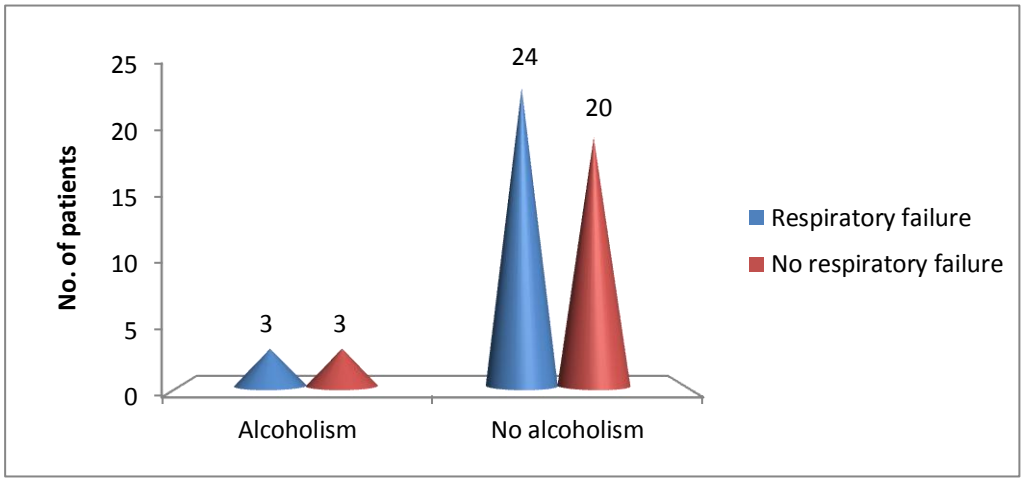


FIGURE 8: GRAPH SHOWING COMPARISON OF ALCOHOLISM AND RESPIRATORY FAILURE

Hence it was found that smoking (p=0.75)/alcoholism (p=1.00) did not influence the development of respiratory failure.

PRECEDING ILLNESSES

Among the 50 patients 19 patients gave history of preceding symptoms and 31 had no such history.

TABLE 11: INCIDENCE OF PRECEDING ILLNESS

	NO. OF PATIENTS	PERCENTAGE
PRECEDING ILLNESS	19	38%
NO PRECEDING ILLNESS	31	62%

Among the 50 patients, 11 had preceding fever, 12 had preceding GIT illness, 9 had preceding respiratory illness, 2 persons had history of recent surgery, one was a hip replacement surgery and the other was following drainage of iliopsoas abscess.

TABLE 12: TYPES OF PRECEDING ILLNESS

PRECEDING ILLNESS	NO OF PATIENTS
FEVER	11
GIT	12
URI	9
OTHERS	2

On analysing each preceding illness, the following results were obtained.

TABLE 13: COMPARISON OF FEVER AND RESPIRATORY FAILURE

	RESPIRATORY FAILURE No. of patients	NO RESPIRATORY FAILURE No of patients
FEVER	6	5
NO FEVER	21	18

Fischer's exact test p=1.00

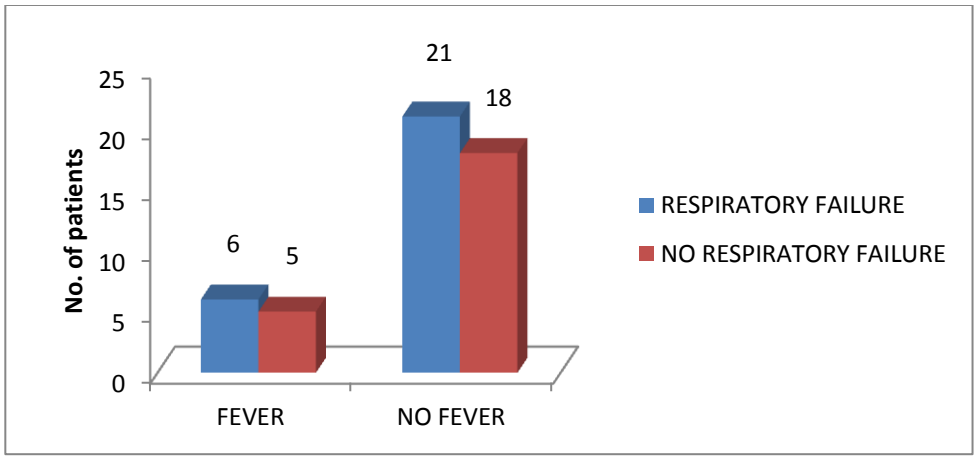


FIGURE 9: GRAPH SHOWING COMPARISON OF FEVER AND RESPIRATORY FAILURE

TABLE 14: COMPARISONOF GIT ILLNESS AND RESPIRATORY FAILURE

	RESPIRATORY FAILURE No. of patients	NO RESPIRATORY FAILURE No. of patients
GIT	5	7
NO GIT	22	16

Fischer's exact test p=0.50

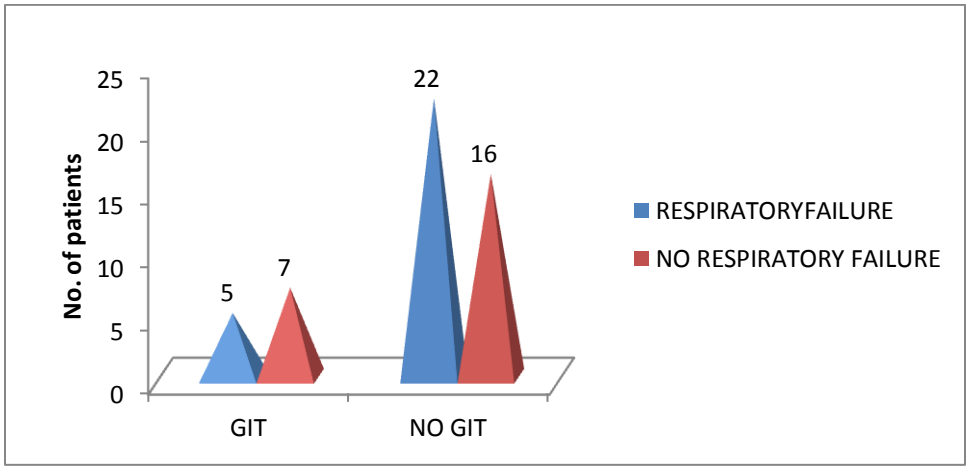


FIGURE 10: GRAPH SHOWING COMPARISON OF GIT ILLNESS AND RESPIRATORY FAILURE

TABLE 15: COMPARISON OF UPPER RESPIRATORY ILLNESS AND RESPIRATORY FAILURE

	RESPIRATORY FAILURE No. of patients	NO RESPIRATORY FAILURE No. of patients
URI	5	4
NO URI	22	19

Fischer's exact test p=1.00

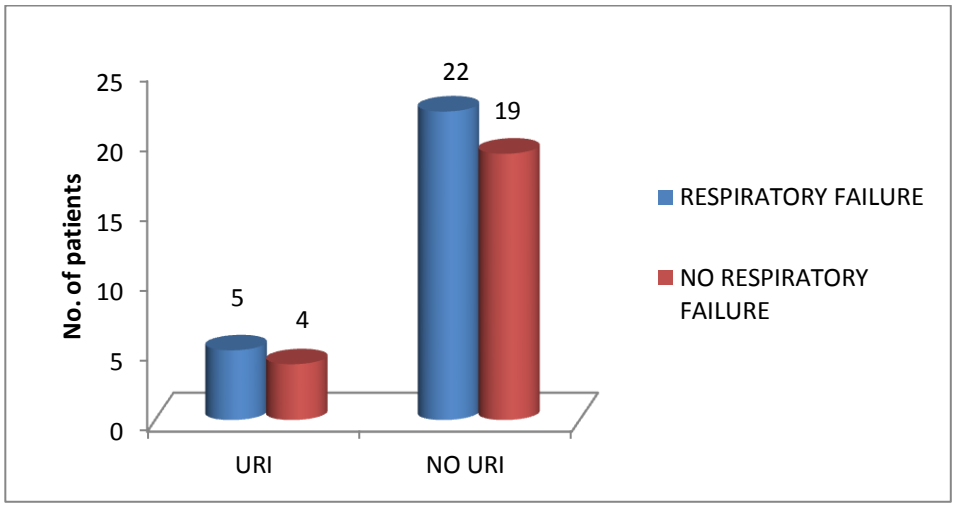


FIGURE 11: GRAPH SHOWING COMPARISON OF URI AND RESPIRATORY FAILURE

Hence no statistically significant association was observed between the presence of preceding GIT illness (p=0.50), URI (p=1.00) or fever (p=1.00) and the development of respiratory failure.

Clinical features analysed with respiratory failure were lowest limb muscle power, neck muscle weakness, bilateral facial weakness, autonomic dysfunction (unexplained blood pressure or heart rate fluctuations or significant bladder or

bowel dysfunction or arrythmias), bulbar weakness (dysarthria, dysphagia or impairment of the gag reflex) and time to peak disability.

MUSCLE POWER

All the patients had varying degrees of quadriparesis, lower limb weakness was more than the upper limb. Muscle power was assessed using MRC grading.

On analysing the occurrence of respiratory failure among patients with various grades of muscle power by MRC grading the following observation was made. The least muscle power among the 4 limbs was taken for analysis.

TABLE 16: INCIDENCE OF RESPIRATORY FAILURE IN VARIOUS MUSCLE POWER

MUSCLE POWER	RESPIRATORY FAILURE (PERCENTAGE)
0/5	60%
1/5	57%
2/5	57%
3/5	56%
4/5	40%

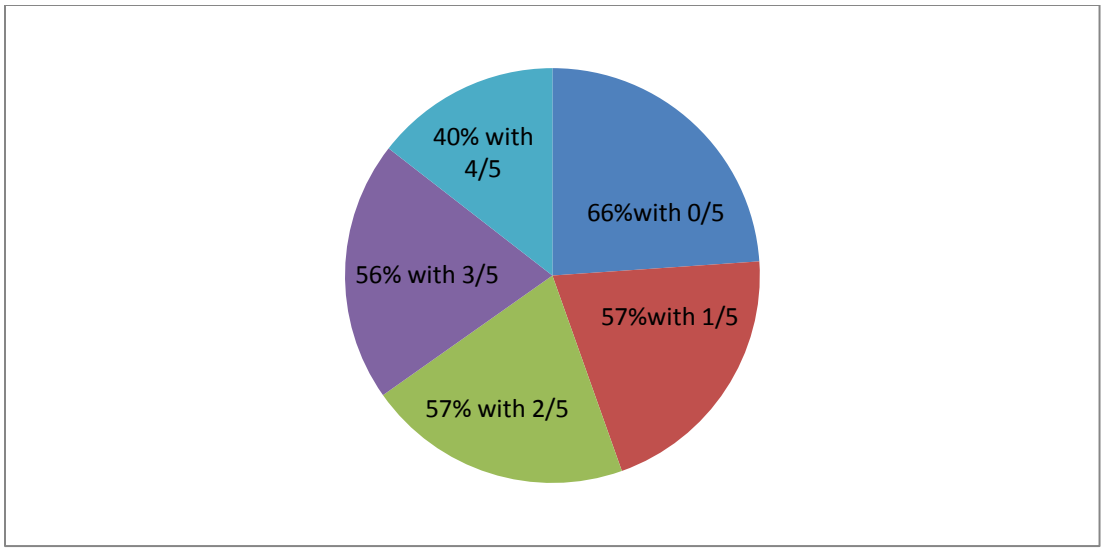


FIGURE 12. PIE DIAGRAM SHOWING PERCENTAGE OF PATIENTS WHO DEVELOPED RESPIRATORY FAILURE WITH DIFFERENT MUSCLE POWER.

Though 66% of patients with 0/5 muscle power developed respiratory failure, no significant association was found on statistical analysis (Fischer's exact test p=1.000)

NECK MUSCLE WEAKNESS

Among the 50 patients 30 had neck muscle weakness of which 20 developed respiratory failure. Hence 67% with neck muscle weakness developed respiratory failure in contrast to 35% of those without neck muscle weakness.

TABLE 17: COMPARISON OF NECK MUSCLE WEAKNESS AND RESPIRATORY FAILURE

	RESPIRATORY FAILURE No. of patients(%)	NO RESPIRATORY FAILURE No. of patients(%)
NECK MUSCLE WEAKNESS	20(67%)	10(33%)
NO NECK MUSCLE WEAKNESS	7(35%)	13(65%)

Fischer's exact test p=0.043

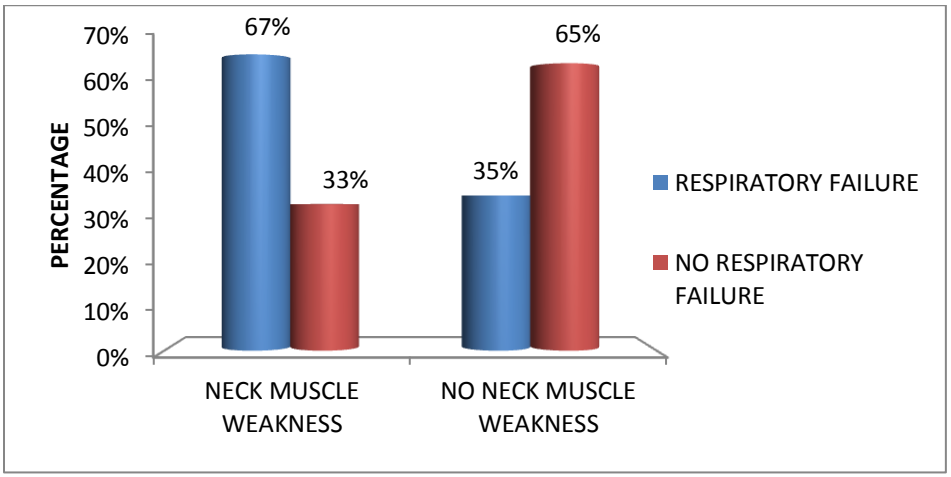


FIGURE 13: GRAPH SHOWING COMPARISON OF NECK MUSCLE WEAKNESS AND RESPIRATORY FAILURE

There was a significant association between the presence of neck muscle weakness and development of respiratory failure (p= 0.043)

FACIAL PALSY, BULBAR PALSY, AUTONOMIC DYSFUNCTION

Among the 50 patients, 14 had only facial weakness, 10 had only bulbar weakness and 10 had both bulbar and facial palsy. About 12 had autonomic dysfunction. The common manifestations of autonomic instability observed in our

study were fluctuating heart rate; episodic or sustained hypertension; orthostatic hypotension; episodic diaphoresis and tachy/bradyarrhythmias.

TABLE 18: INCIDENCE OF FACIALPALSY, BULBAR PALSY AND AUTONOMIC DYSFUNCTION

CLINICAL FEATURES	NO OF PATIENTS
FACIAL PALSY	24
BULBAR PALSY	20
AUTONOMIC DYSFUNCTION	12

Among the patients who had facial weakness, bulbar weakness and autonomic instability, no of patients who required ventilator support subsequently is shown in the following table.

TABLE19: INCIDENCE OF RESPIATORY FAILURE IN FACIAL PALSY, BULBAR PALSY AND AUTONOMIC DYSFUNCTION

	RESPIRATORY FAILURE	NO RESPIRATORY FAILURE
FACIAL	17	7
BULBAR	17	3
AUTONOMIC DYSFUNCTION	12	0

Among the 24 patients with facial weakness 71% developed respiratory failure

TABLE 20: COMPARISON OF FACIAL PALSY AND RESPIRATORY FAILURE

	RESPIRATORY FAILURE No. of patients(%)	NO RESPIRATORY FAILURE No. of patients(%)
FACIAL PALSY	17(71%)	7(29%)
NO FACIAL PALSY	10(38%)	16(62%)

Fischer's exact test, p = 0.026

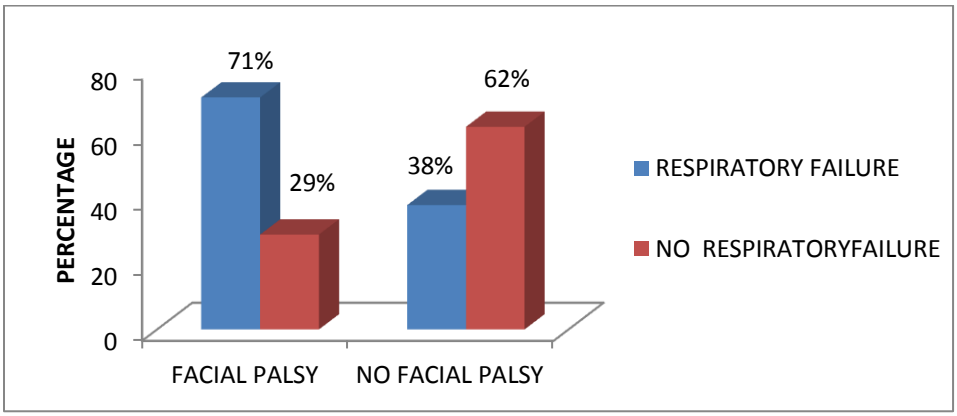


FIGURE 14: GRAPH SHOWING COMPARISON OF FACIAL PALSY AND RESPIRATORY FAILURE

Among the 20 patients with bulbar palsy, 85% developed respiratory failure.

TABLE 21: COMPARISON OF BULBAR PALSY AND RESPIRATORY FAILURE

	RESPIRATORY FAILURE No. of patients(%)	NO RESPIRATORY FAILURE No. of patients(%)
BULBAR PALSY	17(85%)	3(15%)
NOBULBAR PALSY	10(33%)	20(67%)

Fischer's exact test, p=0.0004

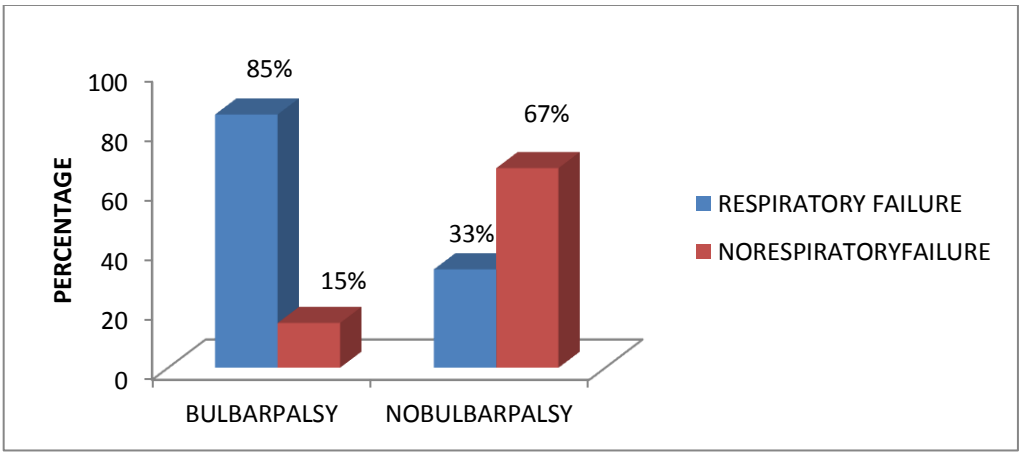


FIGURE 15: GRAPH SHOWING COMPARISON OF BULBAR PALSY AND RESPIRATORY FAILURE

All of the 12 patients with autonomic dysfunction developed respiratory failure

TABLE 22: COMPARISON OF AUTONOMIC DYSFUNCTION AND RESPIRATORY FAILURE

	RESPIRATORY FAILURE No of patients(%)	NO RESPIRATORY FAILURE No of patients(%)
AUTONOMIC DYSFUNCTION	12(100%)	0
NO AUTONOMIC DYSFUNCTION	15(39%)	23(61%)

Fischer's exact test, p= 0.0002

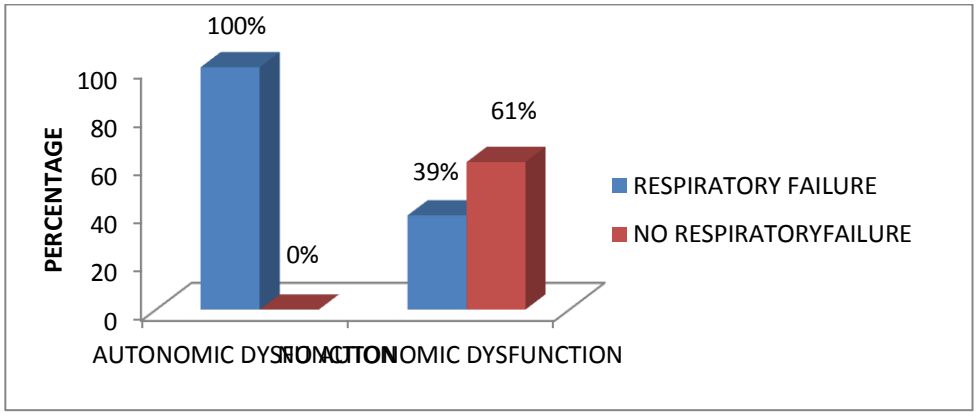


FIGURE 16: GRAPH SHOWING COMPARISON OF AUTONOMIC DYSFUNCTION AND RESPIRATORY FAILURE

TABLE 23:

	RESPIRATORY FAILURE NO.OF PATIENTS(%)	NO RESPIRATORY FAILURE NO.OF PATIENTS(%)	P VALUE (FISCHER'S EXACT TEST)
FACIAL PALSY	**17(71%)**	**7(29%)**	**0.026 (significant)**
BULBAR PALSY	**17(85%)**	**3(15%)**	**0.0004 (extremely significant)**
AUTONOMIC DYSFUNCTION	**12(100%)**	**0**	**0.0002 (extremely significant)**

p value : significant <0.05.

Hence a highly significant association was observed between the presence of facial palsy, bulbar palsy, autonomic instability and the development of respiratory failure.

TIME TO PEAK DISABILITY

Time to peak disability is defined as time to intubation (patients who underwent ventilation), or time to worst score on MRC grading of muscle power (patients who did not undergo ventilation), from the onset of neuropathic symptoms[8].

Among the 50 patients 26 patients had time to peak disability as <7 days and 24 patients had time to peak disability >7 days.

TABLE24. DISTRIBUTION OF TIME TO PEAK DISABILITY

TIME TO PEAK DISABILITY	NO OF PATIENTS	PERCENTAGE
1–7 DAYS	26	52%
>7 DAYS	24	48%

Among the patients with time to peak disability of <7 days, 73% developed respiratory failure in contrast to 33% of those with time to peak disability >7 days

TABLE 25: COMPARISON OF TIME TO PEAK DISABILITYAND RESPIRATORY FAILURE

TIME TO PEAK DIABILITY	RESPIRATORY FAILURE No. of patients(%)	NO RESPIRATORY FAILURE No. of patients(%)
1–7 DAYS	19(73%)	7(27%)
>7 DAYS	16(33%)	8(67%)

$\chi 2$ square test, p=0.0099

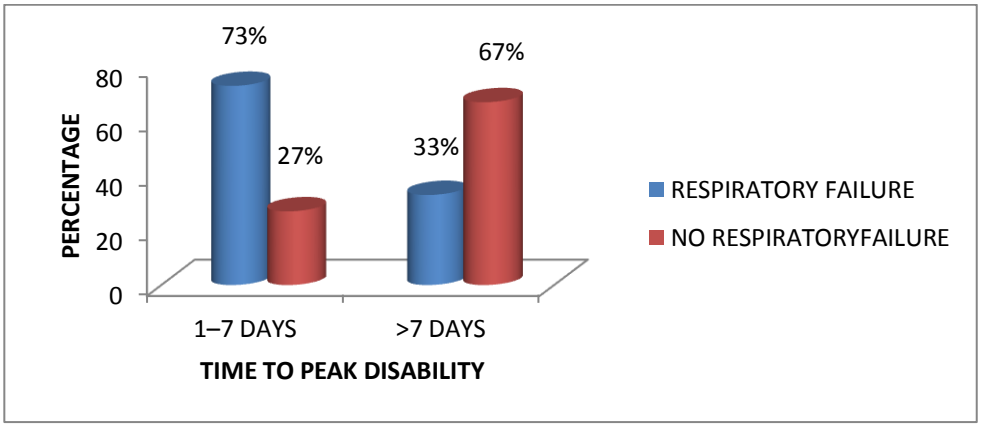


FIGURE 17: GRAPH SHOWING COMPARISON OF TIME TO PEAK DISABILITY AND RESPIRATORY FAILURE

Hence statistically significant association was observed between early time peak disability (<7 days) and the development of respiratory failure (p=0.0099)

Transient sensory, bladder and bowel disturbances were observed in as few as 7 patients. Papilledema was observed in one patient. 1 patient was reactive for HIV.

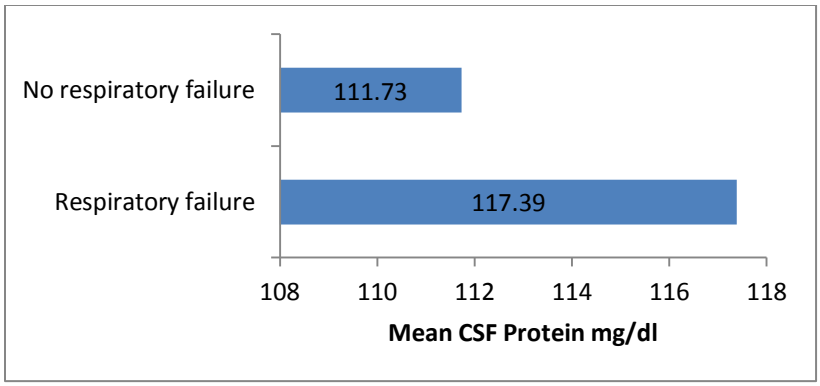
CSF PROTEIN AND SERUM CORTISOL

The CSF protein level was distributed among the 50 patients as follows

TABLE 26: DISTRIBUTION OF CSF PROTEIN LEVEL

CSF PROTEIN LEVEL(mg/dl)	NO. OF PATIENTS
91-100	6
101-110	14
111-120	16
121-130	9
131-140	5

The mean CSF protein level among those patients who developed respiratory failure was 117.39 mg/dl and among those who did not develop respiratory failure was 111.73 mg/dl

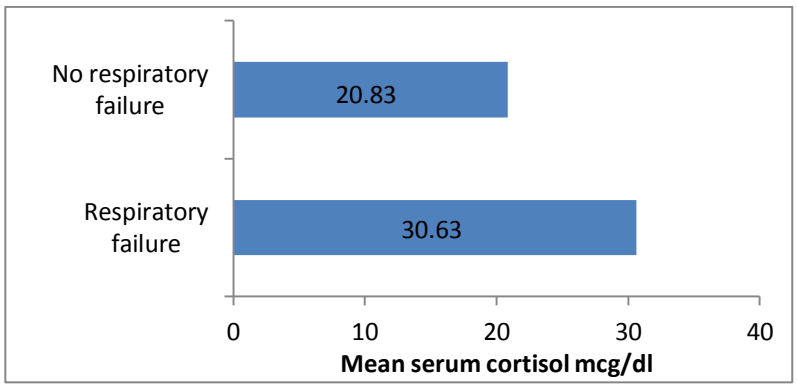


t test p= 0.11

FIGURE 18: BAR DIAGRAM COMPARING CSF PROTEIN LEVEL AND RESPIRATORY FAILURE

On analysing serum protein value and respiratory failure, no significant difference was observed in serum protein value among patients who developed respiratory failure and those who did not (p=0.11).

The mean serum cortisol level was 30.63mcg/dl among those who developed respiratory failure and 20.83mcg/dl among those who did not develop respiratory failure. (Reference range of serum cortisol: 7–10 a.m.: 6.2–19.4 mcg/dl,4–8 p.m.:2.3–11.9 mcg/dl)

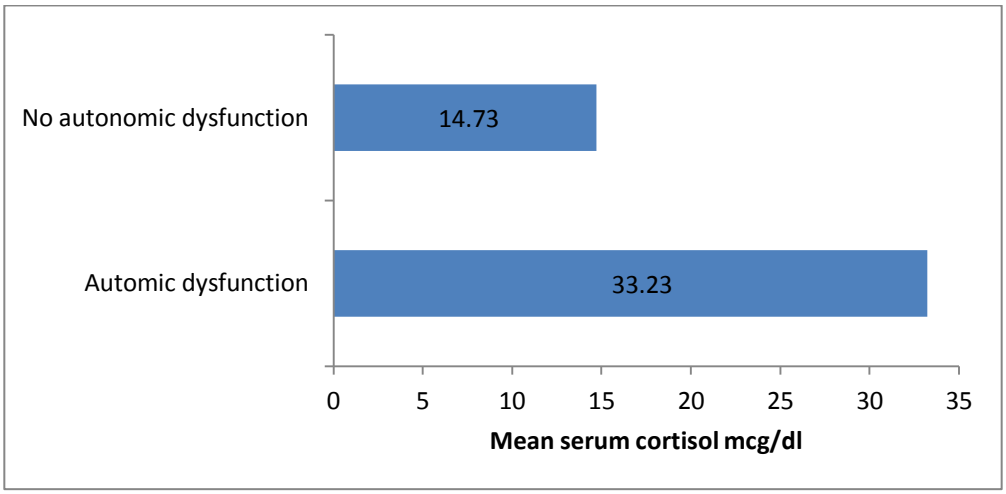


t test p= 0.00015

FIGURE 19: BAR DIAGRAM COMPARING SERUM CORTISOL LEVEL AND RESPIRATORY FAILURE

Baseline serum cortisol level was significantly high in those who developed respiratory failure (p=0.00015).

Mean serum cortisol level among patients with autonomic instability was 33.23mcg/dl, and in those without autonomic instability was14.73 mcg/dl.



t test p=0.004

FIGURE 20: BAR DIAGRAM COMPARING SERUM CORTISOL LEVEL AND AUTONOMIC DYSFUNCTION.

Hence mean serum cortisol level was significantly high in those with autonomic instability (P=0.004).

NERVE CONDUCTION STUDY

We were not able to do NCS in about 9 patients since we couldn't mobilise them for NCS. The commonest finding observed was a radiculopathy, as evidenced by absent or impersistent F waves. Other common observations were prolonged distal motor latency, prolonged F wave latency, reduction in distal CMAP amplitudes with or without temporal dispersion, and slowing of motor conduction

velocity. Electrophysiological data were classified according to Hadden and colleagues[53] definition as primary demyelinating, primary axonal, unexcitable, equivocal, or normal.

Accordingly, 21 had NCS features suggestive of demyelination, 14 had NCS features suggestive of axonal pathology and in 2 it was unexcitable/equivocal. 4 patients had normal NCS features.

TABLE 27: TYPES OF GBS BY NCS

NCS	NO. OF PATIENTS
AIDP	21
AMAN	12
AMSAN	2
NORMAL	4
UNEXCITABLE/EQUIVOCAL	2
TOTAL	41

NCS pattern in patients who developed respiratory failure and in those who did not develop respiratory failure was as shown in the table below.

TABLE 28: TYPES OF GBS (BY NCS) AND RESPIRATORY FAILURE

NCS	RESPIRATORY FAILURE	NO RESPIRATORY FAILURE
AIDP	10	11
AMAN	5	7
AMSAN	1	1
NORMAL	1	3
UNEXCITABLE/EQUIVOCAL	1	1
TOTAL	18	23

Since NCS was not done in 9 patients, we could not proceed with further statistical analysis.

Respiratory function of each patient was assessed daily using SBCT. In our study, average SBC in patients who developed respiratory failure was below 16 on day 1 and there was a rapid decline in SBC compared to a gradual decline in SBC among patients who did not develop respiratory failure as shown below.

FIGURE 21: FIGURE SHOWING THE PATTERN OF DECLINE OF SBC IN RESPIRATORY FAILURE PATIENTS

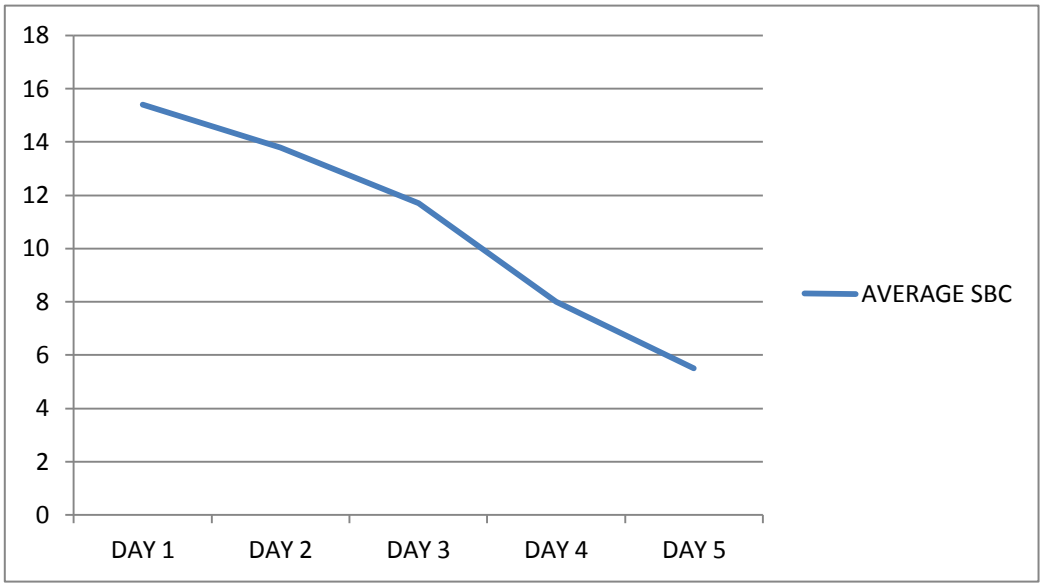
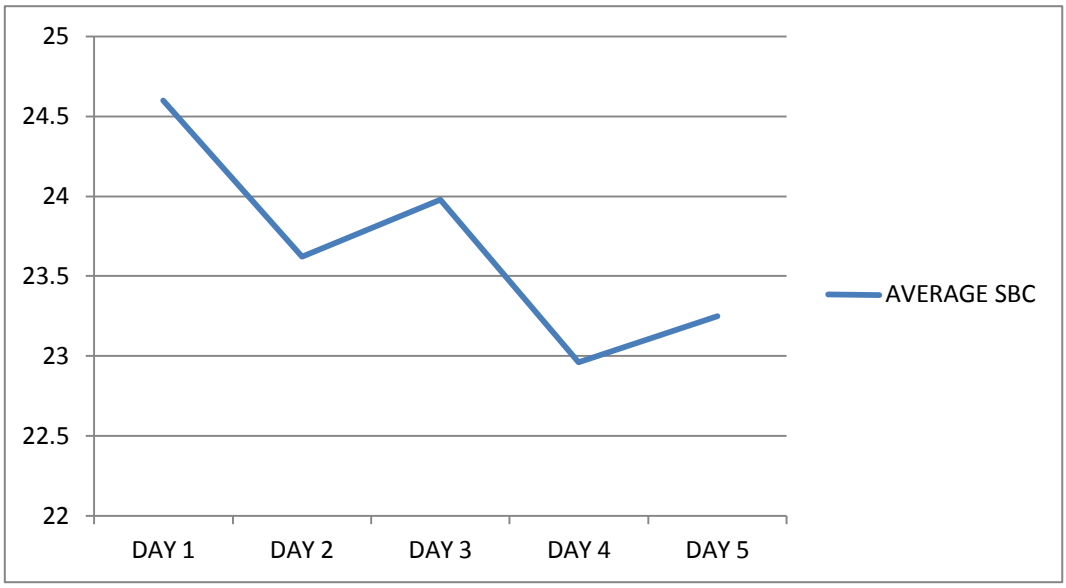


FIGURE 22: FIGURE SHOWING THE PATTERN OF DECLINE OF SBC IN NON-RESPIRATORY FAILURE PATIENTS



DISCUSSION

Neuromuscular respiratory failure is one of the major factors influencing morbidity and mortality in GBS. Successful management of GBS mandates anticipation of respiratory failure and timely intervention.

Our study attempted to identify features that would predict respiratory failure. 50 patients were included in our study. Among them 27 patients developed respiratory failure. The proportion of patients developing respiratory failure and requiring assisted ventilation ranges from 12% in epidemiological series to 30% in hospital-based series[6,7]. In our study it was 54% which could because of our hospital being a tertiary care hospital.

GBS occurs in either sex, with slight male preponderance, and at any age, occasionally including infancy. The mean age of onset is around 40[1].

In our study, age distribution among the 50 patients was such that all of them were between the age group 15–75 years. The peak incidence was in the age group of 31–40 years and the median was 40 years.

36% patients in the age group <30 years, 60% in the age group 30–60 years, 50% in the age group 60–90 years developed respiratory failure. Hence none of the age groups showed increased susceptibility to respiratory failure. Hence age did not influence the development of respiratory failure (p value=0.23).

Of the 50 patients, 31(62%) were males and 19(38%) were females. Hence there was a male predominance. But patients with neither of the sex showed increased propensity to develop respiratory failure. Hence sex did not influence the development of respiratory failure(p value= 0.56).

Hence age and sex did not influence the development of respiratory failure in our study. Similar observations were made by *Nicholas D. Lawn et al*[8] and *Uma Sundar et al*[3].

Nicholas D. Lawn et al studied the influence of co-existing respiratory illnesses on the risk of developing respiratory failure and found an insignificant influence (p=0.28)[8]. In our study we analysed the influence of co-existing respiratory illness as well as diabetes and hypertension and we observed that the presence of these co-existing illnesses did not influence the development of respiratory failure (DM p=0.11,HT p=0.26, Respiratory illness p=0.65).

We also analysed the effect of smoking and alcoholism on the development respiratory failure and we observed that neither of these influence the development of respiratory failure (smoking p=0.75, alcoholism p=1.00).

Among the 50 patients 19 (38%) patients gave history of preceding illnesses. They were either upper respiratory or gastrointestinal symptoms or fever and 2 persons gave history of recent surgery- one was a hip replacement surgery and the other was drainage of iliopsoas abscess.

Winer et al. reported in 1988 that over half of Guillain–Barré syndrome patients experience symptoms of viral respiratory or gastrointestinal infections during the 1–3 weeks prior to the onset of neurological symptoms.

But in our study 38% of patients had such preceding symptoms.

Winer et al. also reported in 1988 that the neurological illness is preceded by symptoms of respiratory tract infection in approximately 40% and gastrointestinal infection in less than 20% in an English series. But in our patients preceding GIT (24%) illness was observed to be more common than respiratory illness(18%).

When each preceding illness was analysed with the development of respiratory failure, we observed that presence of a preceding illnesses did not influence the development of respiratory failure. [p = 0.50(GIT), p=1.00(URI), p=1.00(fever)]. This is in concordance with the observations made by *Uma Sundaret al*[3] in their study done in Mumbai and by *Marie-Christine Durand et al*[4] who analysed preceding GIT illness.

Nicholas D. Lawn et al and *Uma Sundar et al* analysed in their study upper limb weakness with the development of respiratory failure and they observed that upper limb weakness did not influence the development of respiratory failure[8,3]. In contradiction, *Marie-Christine Durand et al* observed that the degree of upper limb weakness was more in ventilated patients but it did not reach statistical significance[4].

In our study, all the patients had varying degrees of quadriparesis, lower limb weakness was more than the upper limb. Muscle power was assessed using MRC grading.

The least muscle power of all 4 limbs was taken for analysis. 66% of patients with 0/5 power, 57% patients with 1/5 power, 57% patients with 2/5 power, 56% with 3/5 power and 40% with 4/5 power developed respiratory failure. Though 66% of patients with 0/5 muscle power developed respiratory failure, the association did not reach statistical significance (p=1.00).

Hence the degree of weakness of limbs did not influence the development of respiratory failure in our study similar to the above studies.

Studies which analysed neck muscle weakness and respiratory failure in GBS gave contradictory results. Significant association (p value: 0.02) was observed in the study done by *Marie-Christine Durand et al* and *Sharshar T.et al* between neck muscle weakness and development of respiratory failure[4,51].

However *Uma Sundar et al* concluded in their study that neck muscle weakness did not predict requirement for mechanical ventilation[3].

In our study out of 30 patients with neck muscle weakness 20(67%) developed respiratory failure (p =0.043).Hence there was a significant association between the presence of neck muscle weakness and the development of respiratory failure.

Among 24 patients with facial weakness 71% developed respiratory failure. (p =0.026, considered statistically significant). Among the 20 patients with bulbar palsy, 85% developed respiratory failure (p=0.0004, considered extremely significant). All of the 12 patients with autonomic instability developed respiratory failure (p = 0.0002, considered extremely significant).

Hence presence of facial palsy, bulbar palsy and autonomic dysfunction was significantly associated with the development of respiratory failure in our study.

This is in concordance with the observations made by *Nicholas D. Lawn* et alin their study done in 1996 that progression to mechanical ventilation was highly likely to occur in those patients with bulbar dysfunction (p = 0.001), bilateral facial weakness(p =0.03), or dysautonomia (p = 0.009)[8].

Similar observations were also made by *Sharshar T. et al.*[51]*and Orlikowski D et al.*[27]*Uma Sundar et al* differed from others stating that bifacial weakness did not influence development of respiratory failure in their study done in Mumbai , but they stated bulbar palsy and autonomic dysfunction as predictors of respiratory failure like in other studies[3].

Time to peak disability was defined as time to intubation (patients who underwent ventilation), or time to worst score on MRC grading of muscle power (patients who did not undergo ventilation), from onset of neuropathic symptoms[8]. In our study 26 patients had time to peak disability as <7 days and among them

73% developed respiratory failure (p = 0.0099).Hence time to peak disability of <7 days was significantly associated with the development of respiratory failure in our study.

This is similar to the observations made by *Nicholas D. Lawn et al* in their study done in 1996, that the requirement for mechanical ventilation was associated with a shorter time to peak disability following the onset of neuropathic symptoms (p= 0.01)[8] and also by *Sharshar T.et al.*at Raymond Poincaré Teaching Hospital, Garches, France.[51]

Elevated CSF protein level of 100-1000mg/dl without pleocytosis is the hallmark of GBS. The CSF is often normal when symptoms have been present for <48 hours. By the end of the first week level of protein is usually elevated[6].

In our study, the mean CSF protein value among those patients who developed respiratory failure was 117.39mg/dl; not significantly different than those who did not develop respiratory failure111.73mg/dl (p=0.11). Hence CSF protein values did not influence the development of respiratory failure in our study. This is similar to the observations of by *Marie-Christine Durand et al* in France in 1996 (p value 0.29)[4].

The mean serum cortisol level was significantly higher among patients with respiratory failure (30.63mcg/dl) than those who did not develop respiratory failure

(20.83mcg/dl); p= 0.00015 considered extremely significant. (Reference range of serum cortisol: 7–10 a.m.: 6.2–19.4 mcg/dl,4–8 p.m.:2.3–11.9 mcg/dl)

Hence high serum cortisol level was significantly associated with the development of respiratory failure in our study. This is similar to the observations made by *Strauss J. et al* at Medical Intensive Care Unit, Raymond Poincaré Teaching Hospital, Garches, France that the baseline plasma cortisol levels were significantly higher in patients, who developed respiratory failure at least 24 hrs later (28.5 +/− 12.1 ng/mL vs. 20.4 +/− 9.6 ng/mL; p = 0.003)[5].

In our study high serum cortisol level was observed among patients with autonomic dysfunction (mean: 33.23 mcg/dl) than those without autonomic dysfunction (mean:14.73 mcg/dl);p=0.04. This is in concordance with the observations made by *Ahmad J. et al.*in 1985 that in cases of Guillain–Barré syndrome with autonomic dysfunction the mean level of plasma cortisol was 27.25 +/ 4.94 micrograms/100 ml while in cases of Guillain–Barré syndrome without autonomic dysfunction it was 11.8 +/− 4.2 micrograms/100 ml[49].

Among the 50 patients, only 1 patient was reactive for HIV by ELISA test.

Nerve conduction study was done in 41patients by using the machine RMS by standard method using surface electrodes. The commonest finding observed in both groups was a radiculopathy, as evidenced by absent or impersistent F waves. Other common observations were prolonged distal motor latency, reduction in

distal CMAP amplitudes with or without temporal dispersion, and slowing of motor conduction velocity. Electrophysiological data were classified according to Hadden and colleagues[53] definition as primary demyelinating, primary axonal, unexcitable, equivocal, or normal. Majority has demyelination features on NCS (AIDP- 21 patients).

Marie-Christine Durand et al stated that neurophysiological testing is helpful for assessing risk of respiratory failure, which is highest in patients with evidence of demyelination. He observed in his study that demyelinating Guillain-Barré syndrome was more common in patients who went on to be ventilated than in those who were not (85% vs. 51%, p=0·0003)[4]. But since we were not able to do NCS in 9 patients we couldn't proceed with further statistical analysis.

Although there is insufficient evidence to recommend a specific method for monitoring respiratory function in patients with GBS, vital capacity is the most studied and used measurement in these patients. Chevrolet and Deleamont identified that a decline in VC of 50% from baseline was associated with subsequent ventilation within 36 hours and a drop in VC to an absolute value less than 1 L was associated with ventilation within 18 hours. Conversely, the serial VC measurements were stable and greater than 40 mL/kg in all patients who did not receive mechanical ventilation[57]. Due to lack of facilities we used serial measurement of single breath count instead of serial vital capacity measurement.

Single breath count test (SBCT) has been used to evaluate the ventilatory status of patients with suspected neuromuscular compromise (e.g., myasthenia gravis, Guillain–Barre syndrome, and botulism) [55]. In general a single breath count of <15 is consistent with significant impairment of the patient's vital capacity[54,55,56]. Respiratory function was assessed in our patients with single breath count. Average SBC of <16 and a rapid decline of SBC was observed in patients who developed respiratory failure subsequently..

Summary

1. No significant difference was observed between patients who developed respiratory failure and those who did not with respect to age, sex, the presence of preceding illnesses, co-morbid illnesses, smoking/ alcoholism and the degree of limb weakness.

2. Significant association was observed between rapid progression of disease (Time to peak disability of <7 days), presence of neck muscle weakness, facial palsy, bulbar palsy, autonomic instability and the development of respiratory failure.Hence presence of these factors either alone or in combination should alert the physicians that respiratory failure is likely to occur.

These factors may be used

A) To decide on admissions in the Intensive care unit and preparation for elective intubation.

B) To refer patients early from a primary health care centre.

C) To educate patients to seek early medical attention.

However the usage of the predictors of respiratory failure in clinical practice is hindered by the fact that the clinical features in GBS do not occur sequentially, for example patients may develop autonomic instability after developing respiratory failure. However when present, before the development of respiratory failure, they are very useful.

3. Results of cerebrospinal fluid analysis were similar in both groups.

4. High baseline serum cortisol level was associated with the development of autonomic instability and respiratory failure. When facilities are available serum cortisol can be used as a valuable tool to anticipate the development of autonomic failure which is an important cause of death in GBS patients.

Patients with high cortisol level may be promptly shifted to intensive care unit for want of continuous monitoring for the development of arrhythmias and the wide variation in blood pressure and pulse rate which are common in patients with autonomic dysfunction.

5. SBC of less than 16 and a rapid decline of SBC was observed in patients who developed respiratory failure. Such findings in a given patient should prompt referral to higher institution and preparation for an elective intubation. SBCT can be used to assess the respiratory function of GBS patients, in hospitals with lack of facilities to measure vital capacity

Limitations of the study:

1. Analysis of the contribution of electrophysiological factors in predicting progression to respiratory failure was limited by the amount of missing data.

2. We could have got more impressive results if the sample size has been large.

CONCLUSION

- Rapid progression of disease (Time to peak disability of <7 days), presence of neck muscle weakness, facial palsy, bulbar palsy, autonomic instability can predict the development of respiratory failure.
- High baseline serum cortisol level can predict the development of autonomic instability and respiratory failure.
- Single breath count of less than 16 and rapid decline of SBC can be used to predict respiratory failure.
- These predictors can be useful in making decisions regarding admission in intensive care unit, preparation for elective intubation, prompt referral to a higher institute equipped with facilities for mechanical ventilation in Guillain-Barre Syndrome patients.

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PROFORMA

Name Age Sex In Patient No.

Occupation Place Income

Date of admission: Date of discharge/death:

h/o GIT illness : Y/N

h/o URI : Y/N

h/o Fever : Y/N

Others : Y/N [h/o vaccination /trauma/surgeries/lymphoma/ drugs/SLE/ Post transplant]

h/o DM : Y/N

h/o HT : Y/N

h/o respiratory diseases :Y/N [COPD /BA/ others]

h/o smoking : Y/N

h/o alcoholism : Y/N

Presenting complaints:

Duration of symptoms on date of admission:

h/o sensory disturbances:

h/o bladder/ bowel disturbances:

h/o altered sensorium/speech disturbances/memory disturbances:

h/s/o cranial nerve involvement:

h/o ataxia:

h/s/o autonomic dysfunction:

a)Postural giddiness(if ambulant):

b)Palpitation/tremors:

c)Excessive sweating/hypohydrosis:

d)Gastrointestinal or genitourinary symptoms:

(nausea,vomiting,constipation,diarrhoea,fecal/urinaryincontinence,urinary retention):

e) h/o dry mouth /dry eyes:

Examination :

Higher motor function abnormality Y/N

Facial weakness: Y/N

Bulbar weakness: Y/N

Other cranial nerves: Y/N

Motor system

DOA to DOPD and DOD

Bulk

Tone

Power : MRC

UL Prox

Distal

LL Prox

Distal

Reflexes Superficial :

Deep tendon reflexes :

Neck muscle weakness Y/N

DOA to DOPD

Single breath count

Breath holding time

Chest expansion

Sensory involvement Y/N

Autonomic system:

Dry Skin/excessive sweating: Y/N

Dry Eye: Y/N Dry Mouth: Y/N

Blood pressure/pulse rate:

Supine

Sitting

Standing (if possible)

Arrhythmias:

Pupillary abnormalities: Y/N

Fundus:

Time to peak disability:

Cardiovascular system:

Respiratory system:

Abdomen:

Complete blood count:

Total count	
Differential Count	
ESR	
Hemoglobin	
Packed Cell Volume	
Platelet Count	

Renal function tests:

Blood Sugar	
Blood Urea	
Serum Creatinine	
Serum Sodium	
Serum Potassium	

Liver function tests:

Total Bilirubin	
SGOT	
SGPT	
SAP	
Total Proteins	
Serum Albumin	

X RAY chest:

ECG

CSF: 1) Protein

2) Sugar

3) Cell count

4) Cytology

ELISA for HIV:

Serum cortisol:

Antinuclear antibody (if needed):

NERVE CONDUCTION STUDY:

DOA: Date of admission, DOPD: Date of peak disability, DOD: Date of discharge/death.

MASTER CHART

S.No.	NAME	AGE	SEX	CO- MORBID ILLNESS			SMOKING	ALCOHOLISM	PRECEDING ILLNESS				TIME TO PEAK INSTABILITY	NECK MUSCLE WEAKNESS	LIMB WEAKNESS	FACIAL WEAKNESS	BULBAR WEAKNESS	AUTONOMIC INSTABILITY	RESPIRATORY FAILURE	CSF PROTEIN	SERUM CORTISOL LEVEL	CSF CELL COUNT	NCS
				DM	HT	OTHER			FEVER	GIT	URI	OTHERS											
1	Durairani	25	F	N	N	N	N	N	N	Y	N	N	8	Y	2	N	N	N	N	108	12.4	Acellular	AIDP
2	Mary	35	F	N	N	Y(BA)	N	N	N	Y	N	N	12	N	3	N	N	N	N	105	31	2-3 lymph	AIDP
3	Rukkammal	50	F	N	N	N	N	N	N	Y	N	N	15	Y	3	N	N	N	N	123	14.05	Acellular	AMAN
4	Nandhagopal	68	M	N	N	N	N	N	N	N	Y	Y	5	Y	4	Y	Y	Y	Y	139	34.12	Acellular	AIDP
5	Vellaiyan	50	M	Y	N	N	Y	Y	N	N	N	N	9	N	1	N	N	N	N	99	14.3	Acellular	AMAN
6	Penecillaiah	38	M	N	N	N	N	N	N	Y	N	N	10	Y	0	N	Y	Y	Y	106	33.28	Occ lymphocytes	AIDP
7	Vidhyadaran	48	M	N	N	N	N	N	Y	N	N	N	6	Y	3	N	Y	Y	Y	96	28.61	Acellular	AMAN
8	Savithri	25	F	N	N	N	N	N	N	Y	Y	N	14	N	4	N	N	N	N	117	30.45	2-3 lymphocytes	AIDP
9	Prabhu	33	M	N	N	N	N	N	Y	N	N	N	5	N	2	Y	Y	N	Y	119	13.83	Acellular	
10	Pushpalatha	42	F	N	N	Y(OLD PT)	N	N	N	N	N	N	3	Y	0	Y	Y	N	Y	105	32.84	Occ lymphocytes	AMSAN
11	Perumal	60	M	Y	Y	N	Y	Y	N	Y	N	N	4	N	3	N	N	N	Y	118	28.2	Acellular	AIDP
12	Christopher	51	M	N	N	N	N	N	Y	N	N	N	5	Y	4	Y	N	N	Y	126	35.32	Occ lymph	AIDP
13	Basheer ahamed	35	M	N	N	N	N	N	N	N	Y	N	8	Y	3	N	Y	N	N	119	34.96	Acellular	AMAN
14	Murthy	15	M	N	N	N	N	N	N	Y	N	Y	1	Y	4	Y	N	N	Y	105	28.34	Acellular	AIDP
15	Shanthi	45	F	N	N	Y(CAD)	N	N	N	N	N	N	4	Y	3	Y	Y	N	Y	128	30.03	Acellular	AMAN
16	Suresh	39	M	Y	N	Y(OLD PT)	Y	N	N	N	N	N	10	N	0	N	N	N	N	119	14.03	Acellular	AIDP
17	Rathinam	65	M	N	Y	N	N	N	Y	N	Y	N	15	Y	4	N	Y	N	N	105	13.86	Acellular	AMAN
18	nazeera	28	F	N	N	N	N	N	N	Y	Y	N	6	Y	3	Y	Y	Y	Y	99	36.05	Acellular	AIDP
19	Balasubramaniu m	74	M	N	N	N	Y	N	Y	N	N	N	9	Y	1	N	Y	Y	Y	134	35.19	Occ lymp	
20	Raja	27	M	N	N	N	N	N	N	N	N	N	8	N	1	N	N	N	N	118	12.99	Acellular	AMAN
21	Arunachalam	59	M	Y	Y	N	N	N	N	N	N	N	7	Y	3	Y	Y	N	Y	129	36.53	Acellular	AIDP
22	Subramanium	48	M	N	N	N	N	Y	N	N	N	N	9	Y	2	N	N	N	Y	94	14.92	Occ lymp	AIDP
23	Gopi	55	M	Y	N	Y(CAD)	Y	N	N	N	N	N	4	Y	2	Y	N	N	Y	121	31.7	Acellular	AIDP
24	Vanmathy	38	F	N	N	N	N	N	Y	Y	Y	N	4	N	3	N	N	N	N	109	13.43	Occ lymp	Normal
25	Venkatesh	30	M	N	N	N	N	N	N	N	N	N	7	Y	4	N	N	N	N	125	25.46	Acellular	Normal

MASTER CHART

S.No.	NAME	AGE	SEX	CO- MORBID ILLNESS			SMOKING	ALCOHOLISM	PRECEDING ILLNESS				TIME TO PEAK INSTABILITY	NECK MUSCLE WEAKNESS	LIMB WEAKNESS	FACIAL WEAKNESS	BULBAR WEAKNESS	AUTONOMIC INSTABILITY	RESPIRATORY FAILURE	CSF PROTEIN	SERUM CORTISOL LEVEL	CSF CELL COUNT	NCS
				DM	HT	Other			FEVER	GIT	URI	OTHERS											
26	Sumathy	45	F	N	N	N	N	N	Y	N	Y	N	4	Y	3	N	Y	Y	Y	130	33.98	Occ lymp	AIDP
27	Balaji	34	M	N	N	N	N	N	N	N	N	N	9	N	2	N	N	N	N	112	13.07	Acellular	AIDP
28	Venda	42	F	Y	N	N	N	N	N	N	Y	N	8	Y	2	N	Y	Y	Y	104	32.69	Acellular	
29	Vinoth	19	M	N	N	N	N	N	Y	Y	N	N	3	Y	3	Y	N	N	N	92	31	Occ lymph	AMAN
30	Punniyakotti	54	M	Y	Y	Y(OLD PT)	Y	Y	N	N	N	N	6	Y	1	Y	Y	Y	Y	137	33.42	Acellular	AIDP
31	Ramaniammal	55	F	Y	Y	N	N	N	N	N	N	N	10	Y	2	Y	N	Y	Y	112	33.96	Occ lymph	
32	Devaki	28	F	N	N	N	N	N	N	N	N	N	9	N	2	N	N	N	N	116	27.95	Acellular	AIDP
33	Kumar	24	M	N	N	N	N	N	N	N	N	N	6	N	1	Y	N	N	Y	120	13.33	Occ lymp	AMSAN
34	Palani	54	M	N	N	N	Y	N	Y	Y	N	N	15	Y	2	N	N	N	N	112	14.23	Acellular	AIDP
35	Mohammed yusuf	45	M	N	N	N	Y	N	N	N	N	N	8	Y	3	Y	N	N	Y	119	27.52	Acellular	AMAN
36	Sankari	36	F	N	N	N	N	N	N	N	N	N	8	N	3	Y	Y	N	Y	94	29.63	Occ lymp	
37	Thomas	44	M	Y	Y	N	Y	Y	N	N	N	N	4	Y	2	N	Y	N	Y	132	31.59	Acellular	AMAN
38	Balammal	35	F	N	N	N	N	N	N	N	N	N	6	N	1	Y	N	N	N	101	28	Occ lymp	AMSAN
39	Vengaiyah	51	M	Y	N	N	Y	N	N	N	N	N	7	N	2	Y	N	Y	Y	114	35.86	Acellular	
40	Sundari	35	F	N	N	N	N	N	N	N	N	N	14	N	3	Y	N	N	N	124	26.89	2-3 lymphocytes	Normal
41	Thiruvengadam	48	M	N	N	N	N	N	Y	N	N	N	6	Y	4	Y	N	Y	Y	112	34.12	Acellular	AMAN
42	Kalaichelvan	39	M	N	N	N	Y	Y	N	N	N	N	6	N	4	N	N	N	N	109	12.99	Occ lymp	AMAN
43	Sathyan	29	M	N	N	N	N	N	N	N	Y	N	8	N	3	Y	Y	N	Y	109	31.6	Acellular	Normal
44	Jansi rani	33	F	N	N	N	N	N	N	N	N	N	14	N	2	N	N	N	Y	104	27.81	2-3 lymphocytes	
45	Vasantha	40	F	N	N	N	N	N	N	N	N	N	5	N	4	Y	N	N	N	121	12.08	Acellular	AIDP
46	Murugan	37	M	Y	N	N	Y	N	N	Y	N	N	6	Y	1	N	Y	N	Y	140	30.03	Acellular	
47	Abdul sherif	52	M	Y	Y	N	N	N	N	N	N	N	10	Y	2	Y	Y	N	N	113	33.9	Occ lymph	AMSAN
48	Nagalakshmi	23	F	N	N	Y(BA)	N	N	Y	N	N	N	7	N	3	Y	N	N	N	105	12.94	Acellular	AIDP
49	Kuppammal	38	F	N	N	N	N	N	N	N	N	N	5	Y	2	N	Y	Y	Y	118	27.51	Acellular	
50	Kannaiyan	62	M	N	Y	N	Y	N	N	N	N	N	9	Y	4	Y	N	N	N	106	34.37	2-3 lymp	AIDP

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No: 04425305301
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CERTIFICATE OF APPROVAL

To
Dr. T. Sugangandhi
PG in MD General Medicine
Madras Medical College, Chennai -3.

Dear Dr. T. Sugangandhi

The Institutional Ethics Committee of Madras Medical College reviewed and discussed your application for approval of the proposal entitled " Clinical , electrophysiological, laboratory predictors (including serum cortisol) of respiratory failure in guillain- barre syndrome patients" No. 20042011.

The following members of Ethics Committee were present in the meeting held on 21.04.2011 conducted at Madras Medical College, Chennai -3.

1.	Prof. S.K. Rajan, MD	-- Chairperson
2.	Prof. V. Kanagasabai MD Dean, Madras Medical College, Chennai-3,	-- Deputy chairman
3.	Prof. A. Sundaram, MD Vice Principal , Madras Medical College, Chennai -3	-- Member Secretary
4.	Prof R. Sathianathan MD	-- Member
5.	Prof R. Nandhini, MD Director, Institute of Pharmacology, MMC, Ch-3	-- Member
6.	Prof. Pregna B. Dolia MD Director , Institute of Biochemistry, MMC, Ch-3	-- Member
7.	Prof. C. Rajendiran .MD Director , Institute of Internal Medicine, MMC, Ch-3	-- Member
8.	Thiru. A. Ulaganathan Administrative Officer, MMC, Chennai -3	-- Layperson
9.	Thiru. S. Govindasamy . BA.BL	-- Lawyer
10.	Tmt. Arnold Soulina	-- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd /. Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information / informed consent and asks to be provided a copy of the final report

Member Secretary, Ethics Committee